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     (FILE 'HOME' ENTERED AT 11:39:03 ON 22 NOV 2004)

     FILE 'REGISTRY' ENTERED AT 11:39:16 ON 22 NOV 2004
L1                STRUCTURE UPLOADED
L2                QUE L1
L3              2 S L2 SSS SAM
L4             72 S L2 SSS FULL

     FILE 'CAPLUS' ENTERED AT 11:40:22 ON 22 NOV 2004
L5             76 S L4
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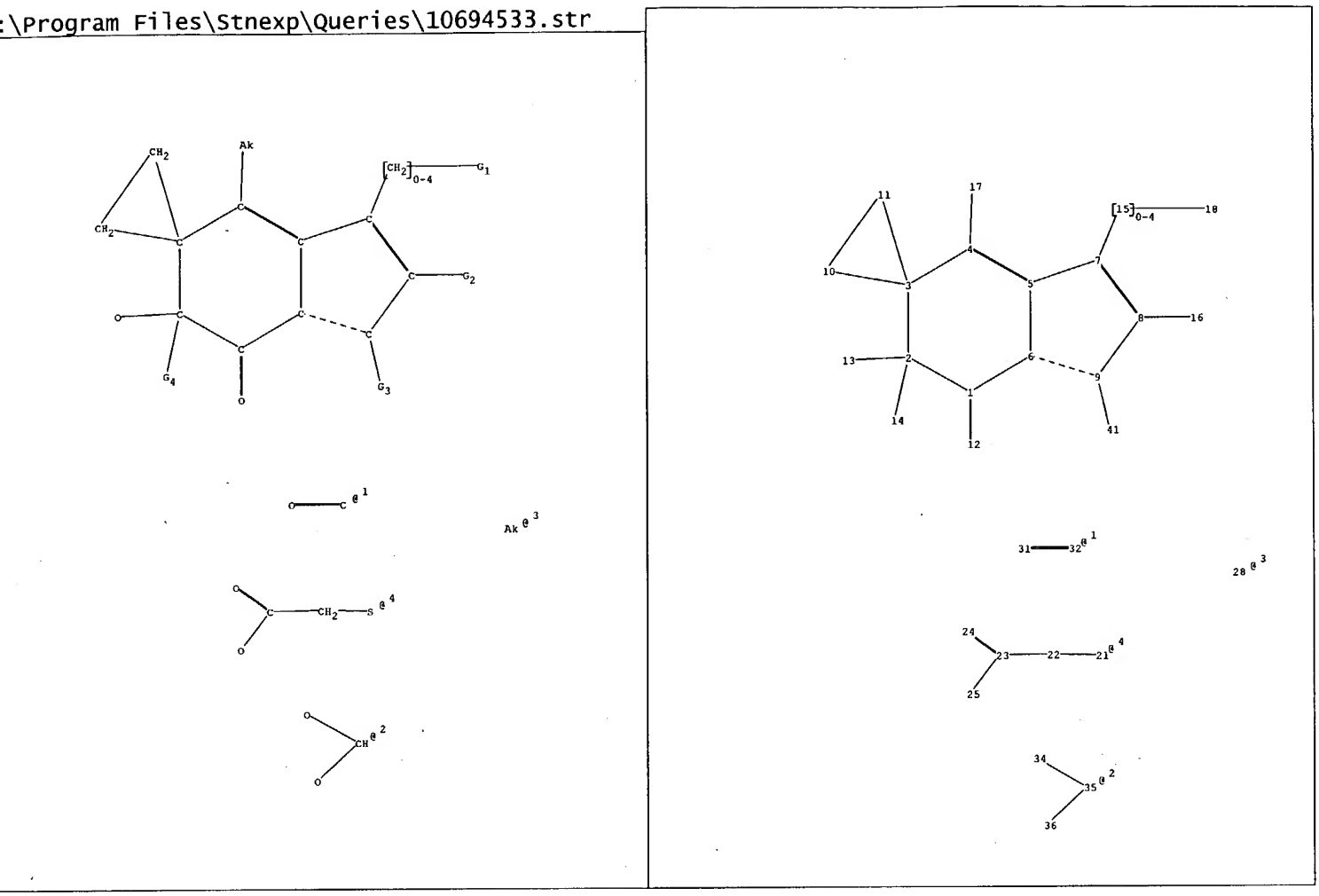


hain nodes :
12 15 16 17 18 21 22 23 24 25 28 31 32 34 35 36 41
ing nodes :
1 2 3 4 5 6 7 8 9 10 11
ing/chain nodes :
13 14
hain bonds :
1-12 4-17 7-15 8-16 9-41 15-18 21-22 22-23 23-24 23-25 31-32 34-35 35-36
ing/chain bonds :
2-13 2-14
ing bonds :
1-2 1-6 2-3 3-4 3-10 3-11 4-5 5-6 5-7 6-9 7-8 8-9 10-11
xact/norm bonds :
1-2 1-6 1-12 2-3 2-13 2-14 3-4 3-10 3-11 4-5 4-17 5-6 5-7 6-9 7-8 8-9
8-16 9-41 10-11 15-18 23-24 23-25 31-32 34-35 35-36
xact bonds :
7-15 21-22 22-23

1:CH,NH,Cy,[*1],[*2]

2:H,[*3]

3:H,[*4]

4:C,O

atch level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom 11:Atom
12:CLASS 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS 21:CLASS 22:CLASS
23:CLASS 24:CLASS 25:CLASS 28:CLASS 31:CLASS 32:CLASS 34:CLASS 35:CLASS 36:CLASS
41:CLASS
lement Count :
Node 17: Limited

C,C1-6

Node 28: Limited
C,C1-6

L5 ANSWER 1 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:817689 CAPLUS
DOCUMENT NUMBER: 141:325783
TITLE: Use of compounds for the prevention of drug-induced cell toxicity
INVENTOR(S): Nykjaer, Anders
PATENT ASSIGNEE(S): Arhus Universitet, Den.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004084876	A2	20041007	WO 2004-DK205	20040325

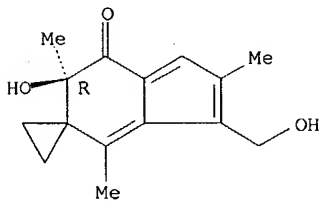
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DK 2003-459 A 20030326

AB The present invention relates to the use of compds. for the manufacture of a medicament for the prophylaxis and/or treatment of induced cell toxicity, such as nephrotoxicity and ototoxicity, in particular where the cell toxicity is induced by a medical treatment. In a preferred embodiment the compds. have at least two nitrogen atoms, more preferably at least two amino groups. The compds. according to the invention are capable of blocking binding of cell toxic compds. to the megalin receptor, and thereby inhibiting uptake of the cell toxic compds. into cells. The invention further relates to novel compds. for use in said treatment, as well as a method for reducing the cell toxicity of cell toxic compds.

IT **158440-71-2**, Irofulven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of compds. for prevention of drug-induced cell toxicity)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 2 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:746756 CAPLUS
TITLE: ATM-dependent CHK2 Activation Induced by Anticancer Agent, Irofulven
AUTHOR(S): Wang, Jian; Wiltshire, Timothy; Wang, Yutian; Mikell, Carmenza; Burks, Julian; Cunningham, Cynthia; Van Laar, Emily S.; Waters, Stephen J.; Reed, Eddie; Wang, Weixin
CORPORATE SOURCE: Mary Babb Randolph Cancer Center, West Virginia University 26506 and MGI Pharma, Inc., Morgantown, WV, 26506, USA
SOURCE: Journal of Biological Chemistry (2004), 279(38), 39584-39592
CODEN: JBCHA3; ISSN: 0021-9258

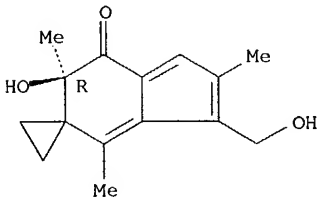
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Irofulven (6-hydroxymethylacylfulvene, HMAF, MGI 114) is one of a new class of anticancer agents that are semisynthetic derivs. of the mushroom toxin illudin S. Preclin. studies and clin. trials have demonstrated that irofulven is effective against several tumor types. Mechanisms of action studies indicate that irofulven induces DNA damage, MAPK activation, and apoptosis. In this study we found that in ovarian cancer cells, CHK2 kinase is activated by irofulven while CHK1 kinase is not activated even when treated at higher concns. of the drug. By using GM00847 human fibroblast expressing tetracycline-controlled, FLAG-tagged kinase-dead ATR (ATR.kd), it was demonstrated that ATR kinase does not play a major role in irofulven-induced CHK2 activation. Results from human fibroblasts proficient or deficient in ATM function (GM00637 and GM05849) indicated that CHK2 activation by irofulven is mediated by the upstream ATM kinase. Phosphorylation of ATM on Ser1981, which is critical for kinase activation, was observed in ovarian cancer cell lines treated with irofulven. RNA interference results confirmed that CHK2 activation was inhibited after introducing siRNA for ATM. Finally, expts. done with human colon cancer cell line HCT116 and its isogenic CHK2 knockout derivative; and expts. done by expressing kinase-dead CHK2 in an ovarian cancer cell line demonstrated that CHK2 activation contributes to irofulven-induced S phase arrest. In addition, it was shown that NBS1, SMC1, and p53 were phosphorylated in an ATM-dependent manner, and p53 phosphorylation on serine 20 is dependent on CHK2 after irofulven treatment. In summary, we found that the anticancer agent, irofulven, activates the ATM-CHK2 DNA damage-signaling pathway, and CHK2 activation contributes to S phase cell cycle arrest induced by irofulven.

IT **158440-71-2**, Irofulven
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ATM-dependent CHK2 activation induced by anticancer agent, irofulven)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 107 THERE ARE 107 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:359100 CAPLUS
TITLE: Evaluation of irofulven (MGI-114) in the treatment of recurrent or persistent endometrial carcinoma: A phase II study of the Gynecologic Oncology Group
AUTHOR(S): Schilder, Russell J.; Blessing, John A.; Pearl, Michael L.; Rose, Peter G.
CORPORATE SOURCE: Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, 19111, USA
SOURCE: Investigational New Drugs (2004), 22(3), 343-349
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective: This multi-center phase II trial was conducted by the Gynecol. Oncol. Group to evaluate the activity and toxicity of irofulven in patients with previously treated adenocarcinoma of the endometrium. Methods: Eligible patients had documented recurrent or persistent endometrial carcinoma after receiving definitive locoregional therapy, and were required to have measurable disease, performance status of 0-2, and adequate bone marrow, hepatic and renal functions prior to study entry.

Patients were allowed one prior chemotherapy regimen. The initial dose of irofulven was 11 mg/m2/day for four days administered i.v. Cycles were repeated every 28 days. Doses were escalated or reduced based on previous cycle toxicity. Results: Twenty-five patients were enrolled onto the trial. There was one (4%) confirmed complete response. Seven (28%) patients had stable disease, with a median duration of 10.4 (range: 4.4-21.6) months. Patients received a median of one (range: 1-5) cycle of protocol treatment. There were three early treatment-related deaths due to renal failure and severe electrolyte disturbances. Two patients experienced grade 4 hematol. adverse effects. Conclusion: Irofulven administered at the dose and schedule used in this trial was minimally active and resulted in significant toxicity.

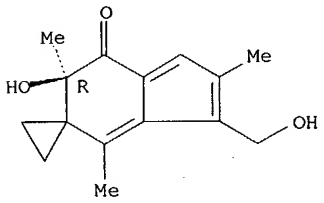
IT INDEXING IN PROGRESS

IT **158440-71-2,** Irofulven
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(irofulven administered at dose schedule of 11 mg/m2/day for 4 days had minimally active antitumor activity and resulted in significant toxicity in patient with recurrent or persistent endometrial carcinoma)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:341654 CAPLUS

DOCUMENT NUMBER: 141:325309

TITLE: Antitumor activity of irofulven monotherapy and in combination with mitoxantrone or docetaxel against human prostate cancer models

AUTHOR(S): van Laar, Emily S.; Weitman, Steven; MacDonald, John R.; Waters, Stephen J.

CORPORATE SOURCE: Research and Development Department, MGI Pharma, Inc., Bloomington, MN, USA

SOURCE: Prostate (New York, NY, United States) (2004), 59(1), 22-32
CODEN: PRSTDS; ISSN: 0270-4137

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB BACKGROUND: Irofulven (6-hydroxymethylacylfulvene, HMAF, MGI 114) is a novel antitumor agent currently undergoing clin. trials in hormone-refractory prostate cancer. This report examines the efficacy of irofulven alone or in combination with mitoxantrone or docetaxel against androgen-independent prostate cancer cell lines. METHODS: To elucidate the activity of irofulven monotherapy and in combination, PC-3 and DU-145 cell lines were utilized in cellular viability assessments and tumor growth inhibition studies. RESULTS: Viability assays with irofulven and mitoxantrone show additive to synergistic activity. Furthermore, irofulven and mitoxantrone in combination exhibit enhanced antitumor activity against PC-3 and DU-145 xenografts. Additive combination effects are also observed when irofulven and docetaxel were tested against PC-3 xenografts and curative activity (8/10 CR) is observed in DU-145 xenografts. CONCLUSIONS: These studies demonstrate that irofulven displays strong activity as monotherapy and in combination with mitoxantrone or docetaxel against androgen-independent prostate cancer in vitro and in vivo; thus, supporting the clin. investigation of irofulven against hormone-refractory prostate cancer.

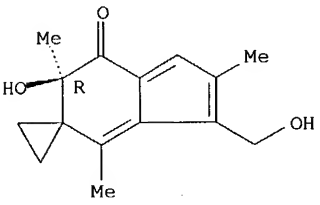
IT **158440-71-2,** Irofulven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(irofulven displays strong antitumor-activity as monotherapy and in combination with mitoxantrone or docetaxel against androgen-independent human prostate cancer PC-3 and DU-145 xenografted into mouse model)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2004:255466 CAPLUS

DOCUMENT NUMBER: 141:253867

TITLE: Activity of irofulven against human pancreatic carcinoma cell lines in vitro and in vivo

AUTHOR(S): van Laar, Emily S.; Roth, Stephanie; Weitman, Steven; MacDonald, John R.; Waters, Stephen J.

CORPORATE SOURCE: MGI Pharma, Inc., Bloomington, MN, 55437-3174, USA

SOURCE: Anticancer Research (2004), 24(1), 59-65
CODEN: ANTRD4; ISSN: 0250-7005

PUBLISHER: International Institute of Anticancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

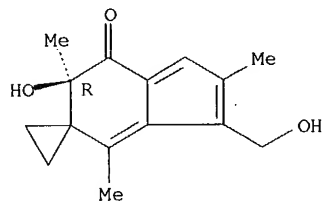
AB Background: Irofulven (MGI 114), a novel antitumor agent synthesized from the natural product illudin S, has a unique mechanism of action involving macromol. adduct formation, S-phase arrest and induction of apoptosis. Materials and Methods: This study utilized MiaPaCa pancreatic xenografts to demonstrate irofulven antitumor activity using either a daily or intermittent dosing schedule. Addnl., irofulven and gemcitabine were tested in vitro and in vivo to assess the anticancer activity of the combination. Results: Both dosing regimens of irofulven demonstrated curative activity against the MiaPaCa xenografts. Similar activity of irofulven on the intermittent schedule was observed at lower total doses compared to the daily dosing schedule. Furthermore, enhanced antitumor activity was observed when irofulven and gemcitabine were combined compared to single agent activity. Conclusion: These results support further clin. characterization of intermittent irofulven dosing schedules and suggest that irofulven combined with gemcitabine may have activity in patients with pancreatic tumors.

IT **158440-71-2**, Irofulven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(HMAF, MGI 114; irofulven significantly reduced tumor weight, tumor growth and combination with gemcitabine enhanced antitumor activity in mouse xenograft model of human pancreatic carcinoma MiaPaCa cell line)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

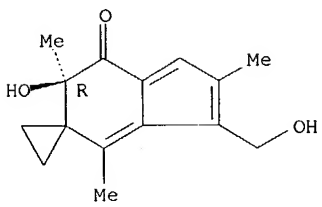
L5 ANSWER 6 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:145046 CAPLUS
DOCUMENT NUMBER: 141:306977
TITLE: NADPH Alkenal/One Oxidoreductase Activity Determines Sensitivity of Cancer Cells to the Chemotherapeutic Alkylating Agent Irofulven
AUTHOR(S): Dick, Ryan A.; Yu, Xiang; Kensler, Thomas W.
CORPORATE SOURCE: Department of Pharmacology and Molecular Sciences, Johns Hopkins School of Medicine, Baltimore, MD, 21205, USA
SOURCE: Clinical Cancer Research (2004), 10(4), 1492-1499
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Illudins S and M are extremely cytotoxic products of the fungus Omphalotus illudens. They were evaluated as possible anticancer chemotherapeutic agents but displayed unfavorable therapeutic indexes. Irofulven (6-hydroxymethylacylfulvene), a less toxic, synthetic derivative of illudin S, has proven very effective in many preclin. and clin. studies. It has been postulated that metabolism via hydrogenation of the 8,9-double bonds of these mols. would unmask the electrophilic, and thus, the toxic nature of their cyclopropyl moieties. Illudins S and M were found to be rapidly metabolized by NADPH-dependent alkenal/one oxidoreductase (AOR) with maximal rates of 115.9 and 44.1 μmol min-1 mg-1, and Kms of 308 and 109 μM, resp. Irofulven was reduced at a much slower rate: Vmax 275 nmol min-1 mg-1 and Km 145 μM. Human 293 cells transfected with an AOR overexpression vector were 100-fold more sensitive than control cells to irofulven, but displayed little differential sensitivity to illudin M. Addition of glutathione to the α,β-unsatd. ketone moiety of illudin M, but not irofulven, occurred readily at physiol. concns. Electrophilic intermediates of irofulven and illudin M that were activated by AOR were trapped with glutathione and identified by high performance liquid chromatog. with tandem mass spectrometry. Samples of the 60 human tumor cell line panel used by the National Cancer Institute to evaluate potential chemotherapeutic compds. were assayed for AOR activity, which correlated pos. with previously determined growth inhibitory measures for irofulven, but not illudin M or S. Collectively, these data indicate that bioactivation of irofulven by AOR plays a predominant role in its chemotherapeutic activity.

IT **158440-71-2**, Irofulven
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AOR activity determined sensitivity of cancer cell to chemotherapeutic alkylating agent irofulven and AOR level, irofulven sensitivity could be greatly influenced by diet and other drug)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2004:69452 CAPLUS
DOCUMENT NUMBER: 140:246127
TITLE: Ab initio structure/reactivity investigations of illudin-based antitumor agents: A model for reaction in vivo
AUTHOR(S): Gregerson, Laura N.; McMorris, Trevor C.; Siegel, Jay

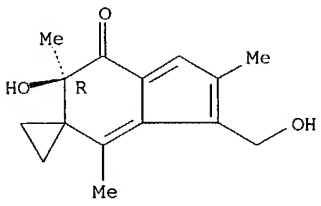
S.; Baldridge, Kim K.
CORPORATE SOURCE: Department of Chemistry, University of California-San Diego, La Jolla, CA, 92093-0358, USA
SOURCE: Helvetica Chimica Acta (2003), 86(12), 4133-4151
CODEN: HCACAV; ISSN: 0018-019X
PUBLISHER: Verlag Helvetica Chimica Acta
DOCUMENT TYPE: Journal
LANGUAGE: English

AB (Hydroxymethyl)acylfulvene (HMAF, irofulven;), a third-generation derivative of a natural product extracted from the mushroom Omphalotus illudens, is selectively toxic towards certain forms of malignant tumors. Conversion of HMAF and cognates to stable aromatic derivs. is triggered by thiol attack in vitro and in vivo. Quantum-chemical methods predict well the structure for several functionalized derivs. of irofulven as compared to known x-ray crystallog. structures. Computational reaction profiles for thiol attack and aromatic rearrangement of irofulven and illudin S, a toxin from which irofulven is derived, provide insight into HMAF's selectivity and toxicity. Methods used include hybrid d.-functional theory (HDFT), Hartree-Fock (HF), and Moller-Plesset second-order perturbation theory (MP2). Solvent effects have been explored by means of the new continuum-solvation method, COSab, presented in an accompanying paper.

IT **158440-71-2**, Irofulven **202799-11-9 670248-55-2**
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ab initio structure/reactivity investigations of illudin-based antitumor agents in a model for reaction in vivo)

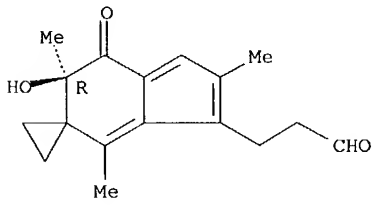
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



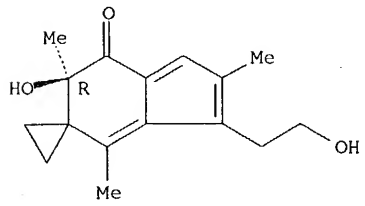
RN 202799-11-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]indene]-3'-propanal, 6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxo-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 670248-55-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(2-hydroxyethyl)-2',4',6'-trimethyl-, (6'R)- (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

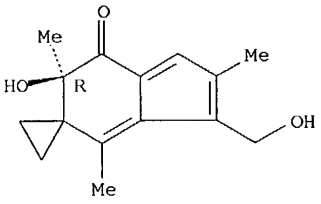
L5 ANSWER 8 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:961321 CAPLUS
DOCUMENT NUMBER: 140:164027
TITLE: Synthesis and Biological Activity of Enantiomers of Antitumor Irofulven
AUTHOR(S): McMorris, Trevor C.; Staake, Michael D.; Kelner, Michael J.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California San Diego, La Jolla, CA, 92093-0506, USA
SOURCE: Journal of Organic Chemistry (2004), 69(3), 619-623
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 140:164027

AB Stereoselective synthesis of (-)-irofulven (I) was achieved by cycloaddn. of (R)-5-chloro-5-methyl-2-cyclopentenone to the 1,3-dipolar intermediate from 1-acetyl-1-(diazoacetyl)cyclopropane. The enantiomer, (+)-irofulven, was prepared in a similar way starting with (S)-5-chloro-5-methyl-2-cyclopentenone. (+)-Irofulven was 5 to 6 times less toxic than (-)-irofulven to adenocarcinoma (MV 522) cells.

IT **158440-71-2P**, Irofulven **283168-03-6P**, Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'S)-
RL: PAC (Pharmacological activity); PNU (Preparation, unclassified); BIOL (Biological study); PREP (Preparation)
(synthesis and biol. activity of enantiomers of antitumor irofulven)

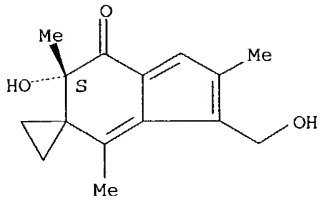
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 283168-03-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:949173 CAPLUS
DOCUMENT NUMBER: 140:362958
TITLE: Preparation and polymerization behavior of polymeric dental restorative materials containing high molecular weight diluent system
AUTHOR(S): Kim, Ohyoung; Chun, Jiyoun; Kim, Yongwoon; Shim, W. Jaewoo
CORPORATE SOURCE: Department of Polymer Science & Engineering, Dankook

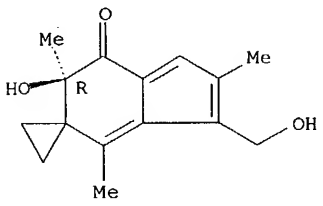
University, Seoul, 140-714, S. Korea
SOURCE: Journal of Industrial and Engineering Chemistry (Seoul, Republic of Korea) (2003), 9(6), 679-685
CODEN: JIECFI; ISSN: 1226-086X
PUBLISHER: Korean Society of Industrial and Engineering Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Preparation of polymeric dental restorative materials (PDRM) showing a lower polymerization shrinkage was carried out using the hybrid-filler and 2,2'-bis-[4-(3-methacryloxy-2-hydroxypropoxy)phenyl]propane resin matrix that is diluted with a high mol. weight dimethacrylate monomer. A visible light system was utilized to activate the resin matrix for the polymerization In order to enhance the miscibility of the inorg. hybrid-filler with organic resin matrix and to conduct the homogeneity of the filler in the PDRM, its surface was hydrophobically treated with γ - methacryloxypropyltrimethoxysilane. The degree of conversion (DC), depth of cure, and polymerization shrinkage of the PDRM were investigated. The results revealed that PDRM prepared herein showed markedly lower polymerization shrinkage values. Besides, regardless of the filler loading, both DC and depth of cure values decreased with an increase in the amount of less flexible diluent in the resin matrix.

IT **158440-71-2**, H-MAF
RL: PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation and polymerization behavior of polymeric dental restorative materials containing high mol. weight diluent system)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



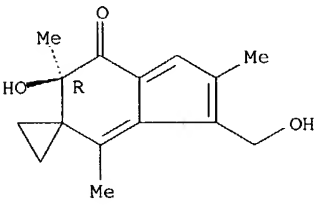
REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:922837 CAPLUS
DOCUMENT NUMBER: 140:112
TITLE: Advanced pancreatic cancer: is there a role for combination therapy?
AUTHOR(S): Kulke, Matthew H.
CORPORATE SOURCE: Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Expert Review of Anticancer Therapy (2003), 3(5), 729-739
CODEN: ERATBJ; ISSN: 1473-7140
PUBLISHER: Future Drugs Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Once thought to be a relatively untreatable disease, pancreatic cancer has recently become a focus of intense clin. research. The systemic administration of gemcitabine (Gemzar) is currently considered the standard first-line treatment for patients with advanced disease. While treatment with gemcitabine has been shown to result in both clin. benefit and prolongation of survival, objective tumor responses are relatively uncommon and median survival times remain short. Several recent efforts have therefore focused on evaluating chemotherapy regimens in which gemcitabine is combined with other cytotoxic drugs. While randomized trials have now confirmed that such combinations are associated with higher response rates, they have not yet clearly demonstrated that combination therapy results in a survival advantage. Increasingly, attention has turned to a number of novel chemotherapeutic and biol. agents that appear promising and are likely to play an important future role in the treatment of patients with this disease.

IT **158440-71-2**, Irofulven
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy for advanced pancreatic cancer)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

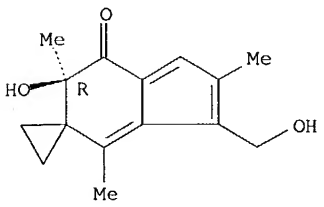


REFERENCE COUNT: 72 THERE ARE 72 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:914799 CAPLUS
DOCUMENT NUMBER: 140:263777
TITLE: Enhanced antitumor activity of irofulven in combination with 5-fluorouracil and cisplatin in human colon and ovarian carcinoma cells
AUTHOR(S): Poindessous, Virginie; Koeppel, Florence; Raymond, Eric; Cvitkovic, Esteban; Waters, Stephen J.; Larsen, Annette K.
CORPORATE SOURCE: Group of Biology and Pharmacogenetics of Human Tumors, CNRS UMR 8113, Ecole Normale Superieure, Cachan and Institut Gustave-Roussy, Villejuif, 94805, Fr.
SOURCE: International Journal of Oncology (2003), 23(5), 1347-1355
CODEN: IJONES; ISSN: 1019-6439
PUBLISHER: International Journal of Oncology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Irofulven (6-hydroxymethylacylfulvene, MGI-114, NSC 683863) is a semisynthetic derivative of illudin S, a natural product obtained from the Omphalotus mushroom. Irofulven has demonstrated potent activity against a broad range of solid tumors in both cellular and xenograft models and has shown promising activity in clin. trials. To guide the clin. use of irofulven, the present study used the MTT viability assay to examine the cytotoxic effects obtained by combining irofulven with two other anticancer agents: cisplatin and 5-fluorouracil (5-FU). The study was carried out with HT-29 and HCT-116 colorectal and A2780 ovarian carcinoma cells as well as with their irofulven- (HT-29/IF2, HCT-116/IF27) or cisplatin-resistant (A2780/CP70) variants. The combinations showed strong sequence specificity. Simultaneous exposure to cisplatin and irofulven was at least additive for four cell lines including the cisplatin-resistant A2780/CP70 ovarian cells which exhibit a multifactorial resistance phenotype. Cisplatin followed by irofulven was additive for parental HCT-116 and A2780 cells whereas irofulven followed by cisplatin was antagonistic in all cellular models. Simultaneous exposure to 5-FU and irofulven was at least additive for all six cell lines. 5-FU followed by irofulven was additive for the parental HT-29 and A2780 cells and synergistic for the irofulven-resistant HCT-116 cell line. Irofulven followed by 5-FU was synergistic for the two ovarian cell lines and additive for the two parental colon cell lines. These studies demonstrate that simultaneous exposure to irofulven and cisplatin is at least additive for most cell lines whereas simultaneous exposure to irofulven and 5-FU is additive to synergistic for all the cell lines tested, including the irofulven- and cisplatin-resistant variants. The enhanced cytotoxicity of irofulven in combination with cisplatin and 5-FU support the clin. application of these regimens.
IT **158440-71-2**, Irofulven
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced antitumor activity of irofulven in combination with 5-fluorouracil and cisplatin in human colon and ovarian carcinoma cells)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

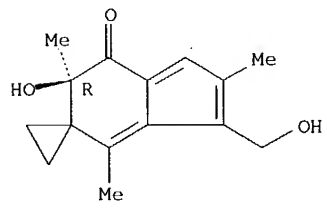
Absolute stereochemistry.



REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:709056 CAPLUS
DOCUMENT NUMBER: 139:285898
TITLE: Phase II study of MGI-114 administered intravenously for 5 days every 28 days to patients with metastatic colorectal cancer
AUTHOR(S): Nasta, Sunita Dwivedy; Hoff, Paulo M.; George, Christopher S.; Neubauer, Marcus; Cohen, Steven C.; Abbruzzese, James; Winn, Rodger; Pazdur, Richard M.
CORPORATE SOURCE: Division of Cancer Medicine, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
SOURCE: American Journal of Clinical Oncology (2003), 26(2), 132-134
CODEN: AJCODI; ISSN: 0277-3732
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We examined the use of MGI-114 (6-hydroxymethyacylfulvene) for the treatment of patients with advanced colorectal carcinoma. Twenty-six patients were enrolled, with a median age of 60 yr (range 41-75); 64% were male and all patients had a performance status of 0 or 1. We administered a dose of 11 mg/m2/d + 5 days every 4 wk. With a median of two cycles (range 0-6) administered, no complete responses or partial responses were observed Four patients had no change in disease (16%); 15 patients (57%) had progressive disease; seven patients were inevaluable (27%). Toxicity was evaluated in 25 of 26 patients. The main toxicities were hematol., including granulocytopenia and thrombocytopenia. Neuropsychiatric adverse events included hallucination (7.7%), depression/anxiety (15.4%), and/or insomnia (19.2%). Given the lack of antitumor activity, further study of MGI-114 in colorectal cancer does not appear warranted.
IT **158440-71-2**, MGI-114
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MGI-114 in patients with metastatic colorectal cancer)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

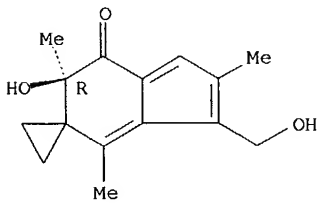
L5 ANSWER 13 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:528831 CAPLUS

DOCUMENT NUMBER: 140:70429
TITLE: Marked activity of irofulven toward human carcinoma cells: comparison with cisplatin and ecteinascidin
AUTHOR(S): Poindessous, Virginie; Koeppel, Florence; Raymond, Eric; Comisso, Martine; Waters, Stephen J.; Larsen, Annette K.
CORPORATE SOURCE: Ecole Normale Superieure, Centre National de la Recherche Scientifique Unite Mixte de Recherche, Laboratory of Biology and Pharmacogenetics of Human Tumors, Cachan and Institut Gustave-Roussy, Villejuif, 94805, Fr.
SOURCE: Clinical Cancer Research (2003), 9(7), 2817-2825
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim was to characterize the activities of irofulven, a novel anticancer agent derived from the mushroom natural productilludin S toward human cancer cells. We have determined the activity spectrum of irofulven toward a human tumor cell panel comprised of 10 different tumor types in comparison with cisplatin and ET-743. We have also evaluated the influence of major resistance mechanisms, such as expression of multidrug resistance-associated drug efflux pumps, cisplatin resistance, loss of p53 function, and absence of mismatch repair on the cytotoxic activity of irofulven. The activity spectrum of irofulven is clearly different from that of ET-743 and cisplatin. Irofulven shows excellent cytotoxicity toward the majority of human carcinoma cell lines tested, but lesser activity toward sarcoma and leukemia cell lines. The cytotoxic activity of irofulven was particularly pronounced toward head and neck, non-small cell lung, colon, and ovary carcinoma cells, as well as toward malignant glioma cell lines. In addition, irofulven displayed good activity toward poorly differentiated, androgen-independent prostate cancer cells and cell lines expressing high levels of the detoxifying enzymes glutathione S-transferase and γ-glutamyl cysteine synthetase. The cytotoxicity of irofulven was not affected by loss of p53 or mismatch repair function, and the drug was not a substrate for multidrug transporters, such as the P-glycoprotein and multidrug resistance protein 1. Irofulven has an unusual activity spectrum with strong activity toward tumor cells of epithelial origin. Furthermore, irofulven is not or only marginally affected by resistance mechanisms limiting the efficacy of other alkylating agents.

IT **158440-71-2**, Irofulven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cytotoxic activity of irofulven toward human carcinoma cells in comparison with cisplatin and ecteinascidin)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

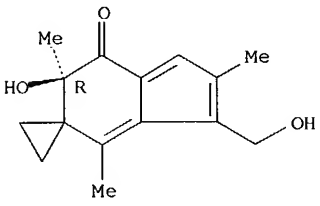


REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 14 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:437144 CAPLUS
DOCUMENT NUMBER: 139:332298
TITLE: Phase I population pharmacokinetics of irofulven
AUTHOR(S): Urien, S.; Alexandre, J.; Raymond, E.; Brain, E.; Smith, S.; Shah, A.; Cvitkovic, E.; Lokiec, F.
CORPORATE SOURCE: Rene Huguenin Cancer Center, Saint-Cloud, Fr.
SOURCE: Anti-Cancer Drugs (2003), 14(5), 353-358
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Our aim was to develop a population pharmacokinetic model for irofulven and to assess covariates that might affect irofulven pharmacokinetics. Irofulven was administered by 5- or 30-min i.v. infusion to cancer patients during a phase I study. Blood samples were collected over 4 h. Plasma samples were analyzed to quantitate irofulven by high-performance liquid chromatog. Population pharmacokinetic anal. was performed using a non-linear mixed effects modeling program, MP2. Fifty-nine patients were available for pharmacokinetic anal. Irofulven plasma concentration-time profiles were best described by a two-compartment pharmacokinetic model. Clearance and central volume of distribution were not significantly influenced by individual characteristics, i.e. body weight (BW), body surface area (BSA), age and gender. Final parameter ests. of clearance and central volume of distribution were 616 l/h and 37 l, resp., resulting in a very short terminal half-life of less than 10 min. A relatively high level of variability was observed in irofulven pharmacokinetics, which was mainly due to a significant residual variability, 39%. For a 30-min irofulven infusion, the optimal sampling schedule for clearance estimation using the Bayesian method was the three time points 0.35-0.45, 0.80 and 1-1.2 h from the beginning of a 30-min infusion. We conclude that after i.v. infusion of irofulven, plasma clearance was high and not dependent upon patient age, gender, BSA or BW.
IT **158440-71-2**, Irofulven
RL: PKT (Pharmacokinetics); BIOL (Biological study)
(phase I population pharmacokinetics of irofulven in cancer patients)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

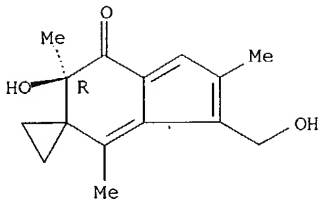
Absolute stereochemistry.



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 15 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:145033 CAPLUS
DOCUMENT NUMBER: 138:280637
TITLE: Irofulven MGI Pharma
AUTHOR(S): Baekelandt, Mark
CORPORATE SOURCE: The Norwegian Radium Hospital, Oslo, 0310, Norway
SOURCE: Current Opinion in Investigational Drugs (PharmaPress Ltd.) (2002), 3(10), 1517-1526
CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER: PharmaPress Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. MGI Pharma is developing irofulven, a semi-synthetic compound derived from illudin S, a toxin from the Omphalotus illudens mushroom, for the potential treatment of refractory and relapsed tumors, including ovarian, prostate, hepatocellular, breast, lung and colon cancers. Phase II trials of the compound as a monotherapy or in combination therapies are ongoing for a number of these indications [448259].
IT **158440-71-2**, Irofulven
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(irofulven for treatment of refractory and relapsed cancer patients)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



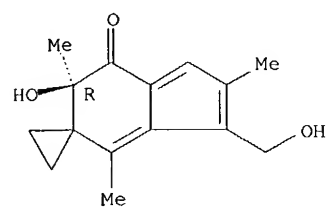
REFERENCE COUNT: 84 THERE ARE 84 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 16 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:91481 CAPLUS
DOCUMENT NUMBER: 139:62790
TITLE: Apoptosis induction by the dual-action DNA- and protein-reactive antitumor drug irofulven is largely Bcl-2-independent
AUTHOR(S): Herzig, Maryanne C. S.; Trevino, Alex V.; Liang, Huiyun; Salinas, Richard; Waters, Stephen J.; MacDonald, John R.; Woynarowska, Barbara A.; Woynarowski, Jan M.
CORPORATE SOURCE: Department of Radiation Oncology, University of Texas Health Science Center, San Antonio, TX, 78245, USA
SOURCE: Biochemical Pharmacology (2003), 65(4), 503-513
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The overexpression of Bcl-2 is implicated in the resistance of cancer cells to apoptosis. This study explored the potential of irofulven (hydroxymethylacylfulvene, HMAF, MGI 114, NSC 683863), a novel DNA- and protein-reactive anticancer drug, to overcome the anti-apoptotic properties of Bcl-2 in HeLa cells with controlled Bcl-2 overexpression. Irofulven treatment resulted in rapid (12 h) dissipation of the mitochondrial membrane potential, phosphatidylserine externalization, and apoptotic DNA fragmentation, with progressive changes after 24 h. Bcl-2 overexpression caused marginal or partial inhibition of these effects after treatment times ranging from 12 to 48 h. Both Bcl-2-dependent and -independent responses to irofulven were abrogated by a broad-spectrum caspase inhibitor. Despite the somewhat decreased apoptotic indexes, cell growth inhibition by irofulven was unaffected by Bcl-2 status. In comparison, Bcl-2 overexpression drastically reduced apoptotic DNA fragmentation by etoposide, acting via topoisomerase II-mediated DNA damage, but had no effect on apoptotic DNA fragmentation by helenalin A, which reacts with proteins but not DNA. Irofulven retains its pro-apoptotic and growth inhibitory potential in cell lines that have naturally high Bcl-2 expression. Collectively, the results implicate multiple mechanisms of apoptosis induction by irofulven, which may differ in time course and Bcl-2 dependence. It is possible that the sustained ability of irofulven to induce profound apoptosis and to block cell growth despite Bcl-2 overexpression may be related to its dual reactivity with both DNA and proteins.

IT **158440-71-2**, Irofulven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(apoptosis induction by the dual-action DNA- and protein-reactive antitumor drug irofulven is largely Bcl-2-independent)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 88 THERE ARE 88 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

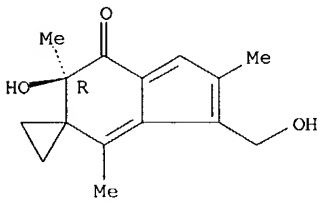
L5 ANSWER 17 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:35691 CAPLUS
DOCUMENT NUMBER: 138:238308
TITLE: Reaction of Irofulven with Zinc and Acid
AUTHOR(S): McMorris, Trevor C.; Moon, Surk-Sik; Kelner, Michael J.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, La Jolla, CA, 92093-0506, USA
SOURCE: Journal of Natural Products (2003), 66(2), 310-312
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 138:238308

AB Reaction of antitumor agent irofulven with zinc and acetic acid yielded several new indene derivs. [I (R = H, OAc, OH), II (R = OH)] as well as the known indene II (R = H). These all have greatly reduced toxicity to human leukemia (HL60) cells compared to irofulven.

IT **158440-71-2**, Irofulven
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation and cytotoxicity of indene derivs. prepared via reaction of irofulven with zinc and acetic acid against human leukemia (HL60 cells))

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 18 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:969167 CAPLUS
DOCUMENT NUMBER: 138:362313
TITLE: Anti-tumour compounds illudin S and Irofulven induce DNA lesions ignored by global repair and exclusively processed by transcription- and replication-coupled repair pathways
AUTHOR(S): Jaspers, Nicolaas G. J.; Raams, Anja; Kelner, Michael J.; Ng, Jessica M. Y.; Yamashita, Yukiko M.; Takeda, Shiunichi; McMorris, Trevor C.; Hoeijmakers, Jan H. J.
CORPORATE SOURCE: Department of Cell Biology and Genetics, Erasmus Medical Center, Rotterdam, 3000 DR, Neth.
SOURCE: DNA Repair (2002), 1(12), 1027-1038
CODEN: DRNEAR; ISSN: 1568-7864
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

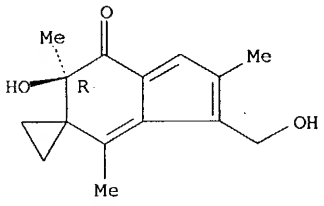
AB Illudin S is a natural sesquiterpene drug with strong anti-tumor activity. Inside cells, unstable active metabolites of illudin cause the formation of as yet poorly characterized DNA lesions. In order to identify factors involved in their repair, we have performed a detailed genetic survey of repair-defective mutants for responses to the drug. We show that 90% of illudin's lethal effects in human fibroblasts can be prevented by an active nucleotide excision repair (NER) system. Core NER enzymes XPA, XPF, XPG, and TFIIH are essential for recovery. However, the presence of global NER initiators XPC, HR23A/HR23B and XPE is not required, whereas survival, repair and recovery from transcription inhibition critically depend on CSA, CSB and UVS, the factors specific for transcription-coupled NER. Base excision repair and non-homologous end-joining of DNA breaks do

not play a major role in the processing of illudin lesions. However, active RAD18 is required for optimal cell survival, indicating that the lesions also block replication forks, eliciting post-replication-repair-like responses. However, the translesion-polymerase DNA pol η is not involved. We conclude that illudin-induced lesions are exceptional in that they appear to be ignored by all of the known global repair systems, and can only be repaired when trapped in stalled replication or transcription complexes. We show that the semisynthetic illudin derivative hydroxymethylacylfulvene (HMAF, Irofulven), currently under clin. trial for anti-tumor therapy, acts via the same mechanism.

IT **158440-71-2**, Irofulven
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor compds. illudin S and Irofulven induce DNA lesions ignored by global repair and exclusively processed by transcription- and replication-coupled repair pathways)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

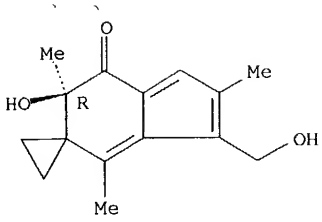
L5 ANSWER 19 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:788015 CAPLUS
DOCUMENT NUMBER: 139:62742
TITLE: Irofulven, a Novel Inhibitor of DNA Synthesis, in Metastatic Renal Cell Cancer
AUTHOR(S): Amato, Robert J.; Perez, Cherie; Pagliaro, Lance
CORPORATE SOURCE: Baylor College of Medicine, Houston, TX, USA
SOURCE: Investigational New Drugs (2002), 20(4), 413-417
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Irofulven (6-Hydroxymethylacylfulvene, MGI-114) is the first of a new class of anticancer compds. the acylfulvenes which are derived from the natural product, illudin S. Irofulven is a potent anticancer agent with activity against a broad range of human tumors in vitro and in vivo. Irofulven covalently binds to DNA, inhibits DNA synthesis and induces apoptosis. Clin. activity has been observed in phase I studies. Because disease stabilizations were observed in kidney cancer patients in the phase I trials, we performed a phase II trial of irofulven in this patient population. Twenty patients were accrued. Irofulven (11 mg per m squared per day) was administered as a 5 min i.v. infusion for 5 consecutive days, and response was evaluated every 8 wk. There were no objective responses. The most common toxicities were nausea, emesis, and thrombocytopenia. Irofulven, at the dose and schedule administered in this trial, showed no effect in metastatic renal cell cancer.

IT **158440-71-2**, Irofulven
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); BIOL (Biological study)
(irofulven efficacy and toxicity in metastatic renal cell cancer)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

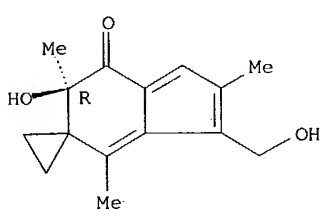
L5 ANSWER 20 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:781153 CAPLUS
DOCUMENT NUMBER: 138:348273
TITLE: Relation between Irofulven (MGI-114) systemic exposure and tumor response in human solid tumor xenografts
AUTHOR(S): Leggas, Markos; Stewart, Clinton F.; Woo, Michael H.; Fouladi, Maryam; Cheshire, Pamela J.; Peterson, Jennifer K.; Friedman, Henry S.; Billups, Catherine; Houghton, Peter J.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
SOURCE: Clinical Cancer Research (2002), 8(9), 3000-3007
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Irofulven is a novel, small mol. weight semisynthetic compound, derived from a family of mushroom toxins known as illudins. This DNA alkylating agent has a chemical structure unlike any other chemotherapeutic agent in clin. use. The mol. is currently being studied in several Phase I, II, and III trials. The objectives of this study were to evaluate the antitumor activity of Irofulven in a panel of 20 pediatric solid tumor xenografts and to relate the Irofulven systemic exposure, defined as area under the concentration time curve, to the antitumor dose associated with tumor regression in the tumor models. Irofulven was administered i.v. daily for 5 days with courses repeated every 21 days for a total of three cycles. The min. ED of Irofulven causing objective regression (≥50% volume regression) of advanced tumors was determined for each of 19 of 20 independently derived tumor models (12 brain tumors, 4 neuroblastomas, and 4 rhabdomyosarcomas). At the maximum tolerated dose for three cycles of treatment (4.6 mg/kg/day) objective regressions were determined in 14 of 18 tumor lines (78%). However, the dose-response relationship was acute. At 2 mg/kg only 3 of 15 tumors tested demonstrated objective regressions, and in 3 addnl. tumors volume regressions were not achieved at a higher dose level (3 mg/kg), hence were not addnl. tested. After administering the maximum tolerated dose (tolerated for one or two cycles of treatment) of Irofulven, 7 mg/kg, to mice bearing sensitive and resistant human tumors plasma concentration-time profiles were determined Tumors were highly sensitive to Irofulven, but the systemic exposure required for a significant rate of objective response in this panel of tumors is in excess of that achievable in patients at tolerable doses, using this schedule of drug administration.

IT **158440-71-2,** Irofulven
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(relation between Irofulven systemic exposure and tumor response in human pediatric solid tumor xenografts)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

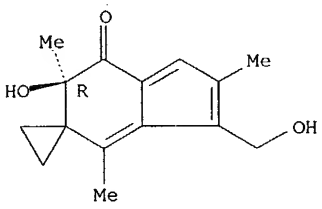
Absolute stereochemistry.



REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 21 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:512410 CAPLUS
DOCUMENT NUMBER: 138:214937
TITLE: A Phase II Study of Irofulven (MGI 114) in Patients with Stage IV Melanoma
AUTHOR(S): Pierson, A. Scott; Gibbs, Peter; Richards, Jon; Russ, Paul; Eckhardt, S. Gail; Gonzalez, Rene
CORPORATE SOURCE: Division of Medical Oncology, Anshutz Cancer Pavilion, University of Colorado Cancer Center, Aurora, CO, USA
SOURCE: Investigational New Drugs (2002), 20(3), 357-362
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Sixteen patients with stage IV melanoma, who were heavily pretreated, received 11 mg/m2/day of i.v. Irofulven for 5 consecutive days every 28 days. There were no objective tumor responses, although 1 patient exhibited stable disease after 4 cycles. The most common toxicities were grade 1/2 nausea, vomiting, fatigue, anemia, and thrombocytopenia. One patient required a dose reduction for an elevated creatinine while another patient required cessation of treatment because of acute ataxia that may have been related to Irofulven. Based upon these data, Irofulven does not demonstrate significant antitumor activity to warrant further investigation in advanced melanoma.
IT **158440-71-2**, MGI 114
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase II study of Irofulven in humans with stage IV melanoma)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 22 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:512397 CAPLUS
DOCUMENT NUMBER: 138:214875
TITLE: Enhanced Antitumor Activity of Irofulven in Combination with Antimitotic Agents
AUTHOR(S): Kelner, Michael J.; McMorris, Trevor C.; Rojas, Rafael J.; Trani, Nicole A.; Velasco, Tami R.; Estes, Leita A.; Suthipinijtham, Pharnuk
CORPORATE SOURCE: Department of Pathology, University of California, San Diego, USA
SOURCE: Investigational New Drugs (2002), 20(3), 271-279
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of this study was to determine the antitumor activity of irofulven when administered in combination with a variety of antimitotic agents. Irofulven in combination with either paclitaxel or docetaxel demonstrated synergistic activity in both the in vitro and in vivo studies. The majority of xenograft bearing animals that received suboptimal (< MTD) doses of irofulven and a taxane demonstrated complete cures. In contrast, in vitro studies produced either an additive or an antagonistic effect when irofulven was combined with other antimitotic agents such as vinca alkaloids, rhizoxin, s-trityl cysteine, or allocolchicine. Xenograft studies of irofulven and vinca alkaloids reflected in vitro results, as

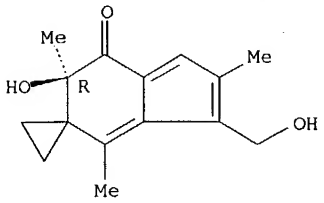
the tumor response in combination treated animals was less than the response in irofulven (monotherapy) treated animals. These results indicate that the therapeutic activity of irofulven is enhanced when combined with taxanes, and warrant further evaluation of these combinations.

IT **158440-71-2**, Irofulven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced antitumor activity of irofulven in combination with antimitotic agents)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 23 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2002:419458 CAPLUS

DOCUMENT NUMBER: 138:19186

TITLE: Irofulven (6-hydroxymethylacylfulvene, MGI 114)-induced apoptosis in human pancreatic cancer cells is mediated by ERK and JNK kinases

AUTHOR(S): Wang, Weixin; Waters, Stephen J.; Macdonald, John R.; Roth, Caleb; Shentu, Shujun; Freeman, James; Von Hoff, Daniel D.; Miller, Alexander R.

CORPORATE SOURCE: Department of Surgery, University of Texas Health Science Center at San Antonio, San Antonio, TX, 78229, USA

SOURCE: Anticancer Research (2002), 22(2A), 559-564
CODEN: ANTRD4; ISSN: 0250-7005

PUBLISHER: International Institute of Anticancer Research

DOCUMENT TYPE: Journal

LANGUAGE: English

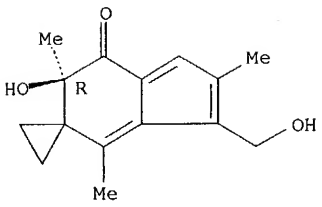
AB Pancreatic carcinoma resists chemotherapeutic mediation of apoptosis. Irofulven (MGI 114, 6-hydroxymethylacylfulvene) is a novel illudin S analog that we have shown to induce caspase-mediated apoptosis in pancreatic carcinoma cell lines. Western blot anal. and kinase assays were used to demonstrate the activation of Erk 1/2 and JNK-1 kinases following Irofulven administration in the presence and absence of selective kinase inhibitors. Irofulven activates JNK1 and Erk1/2, but not p38. The addition of the MAPK inhibitors, SB202190 and PD98059 (targeting JNK1 and Erk1/2 activation, resp.), prevents kinase activation and blocks Irofulven-induced activation of caspases -3, -7, -8 and -9. Blockade of either JNK1 or Erk1/2 results in a 50% decrease in apoptosis in MiaPaCa-2 cells treated with Irofulven. Our data demonstrated that JNK1 and Erk1/2 are activated by Irofulven treatment and that blockade of either MAPK subfamily decreases apoptosis by rendering Irofulven incapable of inducing caspase activation.

IT **158440-71-2**, Irofulven
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(irofulven (6-hydroxymethylacylfulvene, MGI 114)-induced apoptosis in human pancreatic cancer cells is mediated by ERK and JNK kinases)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



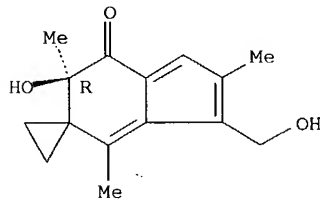
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 24 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:409259 CAPLUS
DOCUMENT NUMBER: 136:406884
TITLE: Ibuprofen-aspirin and hydroxymethylacylfulvene analogs
INVENTOR(S): Guttag, Alvin
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 7 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2002065254	A1	20020530	US 2001-954853		20010918
US 6436916	B2	20020820			
US 2003008833	A1	20030109	US 2002-219960		20020815
PRIORITY APPLN. INFO.:			US 2000-239255P	P	20001012
			US 2001-954853	A2	20010918
			US 2001-327282P	P	20011005

OTHER SOURCE(S): MARPAT 136:406884
AB Ibuprofen-aspirin compds. useful in treating aspirin or ibuprofen-treatable conditions and hydroxymethylacylfulvene analogs useful as antitumor drugs are described. Thus, p-isobutylhydratropic acid ester with salicylic acid was prepared by the reaction of p-isobutylhydratropoyl chloride with salicylic acid in anhydrous ether. A typical formulation for a tablet was prepared from microcryst. cellulose 130, modified starch 20, Mg stearate 5.5, polyvinylpyrrolidone 22, stearic acid 30, and p-iso-Bu hydratropic acid ester of salicylic acid 500 mg.
IT **158440-71-2D**, analogs
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ibuprofen-aspirin derivs. and hydroxymethylacylfulvene analogs for pharmaceuticals)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 25 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:318619 CAPLUS
DOCUMENT NUMBER: 138:117248
TITLE: Enhanced antitumor activity of irofulven in combination with thiotepa or mitomycin C
AUTHOR(S): Kelner, Michael J.; McMorris, Trevor C.; Rojas, Rafael J.; Trani, Nicole A.; Estes, Leita
CORPORATE SOURCE: Department of Pathology 8320, UCSD Medical Center, San Diego, CA, 92103, USA
SOURCE: Cancer Chemotherapy and Pharmacology (2002), 49(5),

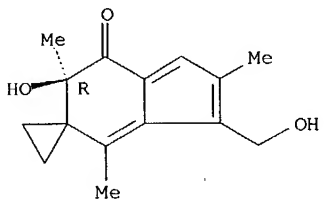
412-418
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The potential use of irofulven in combination with aziridine-containing chemotherapeutic agents was evaluated. Human lung carcinoma MV522 cells and BALB/c athymic mice bearing MV522 xenografts were used to evaluate the activity of irofulven in combination with aziridine-containing drugs. Irofulven in combination with either thiotepa or mitomycin C demonstrated a strong synergistic (supraadditive) activity, both in vitro and in vivo, that exceeded results obtained with monotherapy at the same or higher concns./doses of these agents. The majority of xenograft-bearing animals that received subtoxic doses of irofulven, and either thiotepa or mitomycin C, demonstrated a complete cure. In contrast, there was no detectable synergistic activity between irofulven and other aziridine-containing drugs, including diaziquinone and thiotepa metabolites such as TEPA or AZD [not defined]. These results indicate that the therapeutic activity of irofulven is enhanced when combined with mitomycin C or thiotepa, and further evaluation of these combinations is therefore warranted.

IT **158440-71-2**, Irofulven
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of irofulven in combination with thiotepa or mitomycin C against human lung carcinoma)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 26 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:213222 CAPLUS
DOCUMENT NUMBER: 137:226280
TITLE: Irofulven induces apoptosis in breast cancer cells regardless of caspase-3 status
AUTHOR(S): Herzig, Maryanne C. S.; Liang, Huiyun; Johnson, Anne E.; Woynarowska, Barbara; Woynarowski, Jan M.
CORPORATE SOURCE: Cancer Therapy and Research Center, The University of Texas, San Antonio, TX, USA
SOURCE: Breast Cancer Research and Treatment (2002), 71(2), 133-143
CODEN: BCTRD6; ISSN: 0167-6806
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Caspase-3 deficiency can limit the efficiency of pro-apoptotic anticancer treatments. Irofulven (hydroxymethylacyl-fulvene, HMAF, MGI 114, NSC 683863) is an antitumor drug, currently in a Phase III and multiple Phase II trials, which can differentiate between tumor and normal cells in apoptosis induction. This study investigated whether apoptosis induced by irofulven requires caspase-3. Irofulven action was compared in breast cancer cells differing in caspase-3 status: deficient MCF-7 cells and proficient MDA-MB-231 cells and in normal human mammary epithelial cells, HMEC. Irofulven induces significant, concentration and time-dependent apoptotic DNA fragmentation in breast cancer cell lines, regardless of caspase-3 status. After 12, 24 and 48 h incubation at 1 μM irofulven (.apprx. 3 + GI50), fragmented DNA comprised 3.7, 14.1 and 34.6% and 8.4, 12.6 and 20.3% of total DNA in MCF-7 and MDA-MB-231 cells, resp. Cell viability (trypan blue exclusion) remained largely unaffected during the first 24 h but decreased markedly after 48 h, indicating secondary

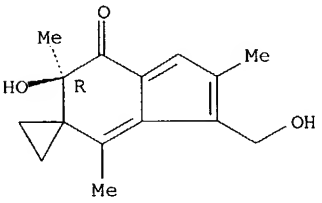
necrosis. Net losses in cell nos. were apparent at 48 h. Normal HMEC cells were refractory to 1 μM drug with only .apprx.3-9% fragmented DNA after 12-48 h, although apoptosis was observed at drug levels > 3 μM. The broad-spectrum caspase inhibitor Z-VAD-fmk inhibited irofulven-induced apoptosis of all cell lines at 20 μM with nearly complete abrogation of apoptosis at 100 μM. Irofulven treatment resulted in marginal caspase-3 processing in MDA-MB-231 and HMEC cells. These results indicate that whereas the caspase cascade mediates irofulven- induced apoptosis, caspase-3 is dispensable.

IT **158440-71-2**, Irofulven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(irofulven induces apoptosis in breast cancer cells regardless of caspase-3 status)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 27 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:855439 CAPLUS
DOCUMENT NUMBER: 137:163220
TITLE: Phase I clinical and pharmacokinetic trial of irofulven
AUTHOR(S): Thomas, James P.; Arzoomanian, Rhoda; Alberti, Dona; Feierabend, Chris; Binger, Kimberly; Tutsch, Kendra D.; Steele, Thomas; Marnocha, Rebecca; Smith, Charlotte; Smith, Sheri; MacDonald, John; Wilding, George; Bailey, Howard
CORPORATE SOURCE: University of Wisconsin, University of Wisconsin Comprehensive Cancer Center and Department of Medicine, Madison, WI, 53792, USA
SOURCE: Cancer Chemotherapy and Pharmacology (2001), 48(6), 467-472
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: To evaluate the clin. tolerability of a new schedule of 6-hydroxymethylacylfulvene (irofulven, MGI 114, HMAF, NSC 683863), a semisynthetic sesquiterpene derived from the cytotoxic mushroom metabolite illudin S. Irofulven has been shown to induce DNA damage and apoptosis in vitro and has shown activity in a number of human tumor xenograft models. A number of drug-resistant cell lines including those that express the mdr phenotype, retain sensitivity to irofulven. Methods: We conducted a phase I trial of irofulven given as an i.v. infusion (30 min) on a daily +5 schedule every 28 days. A total of ten patients were enrolled and treated at three dose levels, 6, 8, and 11 mg/m2 per day. Results: Irofulven reached steady-state concns. during the 30-min infusions with biexponential kinetics. Irofulven disappeared rapidly from plasma and was detectable for only 15-30 min after the end of the infusion. The mean half-life was 4.91 min and the mean clearance was 4.57 l/min per m2. Peak plasma concns. of irofulven of approx. 300 ng/mL were achieved. Pharmacokinetic parameters did not differ significantly from day 1 to day 5. Irofulven was highly emetogenic. Other prominent toxicities included anorexia and fatigue. One case of delayed-onset metabolic acidosis possibly secondary to irofulven was observed No other renal or metabolic toxicity was encountered. One patient experienced a late-onset grade 3 extravasation skin injury thought to be secondary to extravasation of irofulven. Minimal marrow suppression was observed No objective tumor responses were observed Conclusions: The recommended phase II dose on this

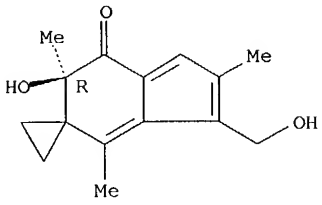
schedule is 6 mg/m2.

IT **158440-71-2**, Irofulven
RL: ADV (Adverse effect, including toxicity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase I clin. and pharmacokinetic trial of irofulven)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 28 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:797630 CAPLUS

DOCUMENT NUMBER: 137:119120

TITLE: Activity of irofulven (6-hydroxymethylacylfulvene) in the treatment of glioblastoma multiforme-derived xenografts in athymic mice

AUTHOR(S): Friedman, Henry S.; Keir, Stephen T.; Houghton, Peter J.; Lawless, Amy A.; Bigner, Darell D.; Waters, Stephen J.

CORPORATE SOURCE: Department of Surgery, Duke University Medical Center, Durham, NC, 27710, USA

SOURCE: Cancer Chemotherapy and Pharmacology (2001), 48(5), 413-416
CODEN: CCPHDZ; ISSN: 0344-5704

PUBLISHER: Springer-Verlag

DOCUMENT TYPE: Journal

LANGUAGE: English

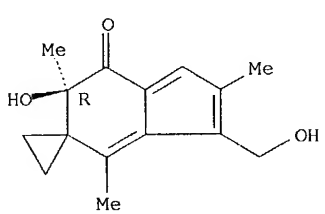
AB Purpose: This study was conducted to define the activity of irofulven in the treatment of a series of xenografts derived from human glioblastoma multiforme growing s.c. and intracranially in athymic nude mice. Methods: Athymic mice bearing s.c. or intracranial tumors were treated with irofulven at a 10% LD with responses compared to tumor-bearing mice treated with drug vehicle. Results: Irofulven was active against all tumor lines tested with growth delays ranging from 5.6 to 81.6 days (all values statistically significant, $P \leq 0.001$). Irofulven also produced a statistically significant ($P \leq 0.001$) increase in the median survival of mice bearing D-456 intracranial xenografts with a 162% increase in median survival. Conclusions: Irofulven is active in a spectrum of human glioblastoma multiforme-derived xenografts and evaluation in patients with this neoplasm is warranted.

IT **158440-71-2**, Irofulven
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of irofulven in the treatment of glioblastoma multiforme-derived xenografts in athymic mice)

RN 158440-71-2 CAPLUS

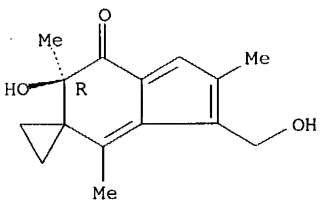
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 29 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:706060 CAPLUS
DOCUMENT NUMBER: 136:31401
TITLE: Phase II trial of irofulven (6-hydroxymethylacylfulvene) for patients with advanced renal cell carcinoma
AUTHOR(S): Berg, William J.; Schwartz, Lawrence; Yu, Richard; Mazumdar, Madhu; Motzer, Robert J.
CORPORATE SOURCE: Genitoury Oncology Service, Division of Solid Tumor Oncology, Department of Medicine, Cornell University Medical College, New York, NY, USA
SOURCE: Investigational New Drugs (2001), 19(4), 317-320
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The aim of this study was to determine the antitumor activity of irofulven (6-hydroxymethylacylfulvene) in patients with advanced renal cell carcinoma (RCC). Eligible patients had advanced renal cell carcinoma with bidimensionally measurable disease, a Karnofsky performance status of at least 70, life expectancy of greater than three months, no prior treatment with chemotherapy, and no evidence of brain metastases. Irofulven was administered at a dose of 11 mg/m2 by 5-min i.v. infusion, on 5 consecutive days. Cycles were repeated every 28 days. Thirteen patients were enrolled in this study and 12 were evaluable for response. Of the twelve evaluable patients, no major responses were achieved. Eight patients had stable disease as best response. Toxicity included myelosuppression and gastrointestinal side effects. At the dose and schedule used in this trial, irofulven did not produce clin. response in RCC.
IT **158440-71-2**, Irofulven
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(irofulven (6-hydroxymethylacylfulvene) for treatment of advanced renal cell carcinoma in humans)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

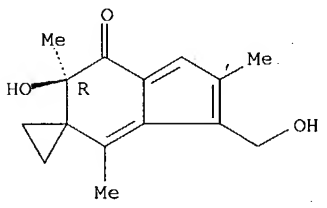
L5 ANSWER 30 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:706056 CAPLUS
DOCUMENT NUMBER: 136:379568
TITLE: Changes in prostate-specific antigen (PSA) level correlate with growth inhibition of prostate cancer cells treated in vitro with a novel anticancer drug, irofulven
AUTHOR(S): Woynarowska, Barbara A.; Higdon, Arlene L.; Munoz, Ruben M.; Bushong, Perry; Waters, Stephen J.
CORPORATE SOURCE: Department of Radiation Oncology, The University of Texas Health Science Center, San Antonio, TX, USA
SOURCE: Investigational New Drugs (2001), 19(4), 283-291
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Irofulven (hydroxymethylacylfulvene, HMAF, MGI 114) is a novel agent with alkylating activity and a potent inducer of apoptosis. It is currently undergoing Phase II clin. trials for several tumor types, including hormone-refractory prostate cancer. Reduction of serum prostate-specific

antigen (PSA) levels has been proposed as a generally useful endpoint for evaluating the antitumor efficacy of treatments for prostate cancer. However, the utility of PSA as a marker of tumor cell burden could be compromised, if drugs directly affected PSA secretion and/or expression. In these studies, we evaluated the effects of irofulven on PSA protein and mRNA levels during the course of treatment of prostate tumor cells in vitro. The rate of PSA secretion (normalized per equal cell number) by control and drug treated cells was similar, as determined by a solid phase, two-site immunoradiometric assay. Consistent with the lack of effect of irofulven on PSA protein level, the drug does not appear to affect the expression of PSA mRNA (on a per cell basis) as assessed by RT-PCR. Thus, changes in PSA secretion and expression appear to reflect irofulven-induced cell growth inhibition rather than reflecting a direct effect of the drug on PSA. These results suggest that PSA should be a reasonable marker of tumor burden in irofulven-treated prostate cancer patients.

IT **158440-71-2**, MGI 114
RL: DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(changes in prostate-specific antigen (PSA) level correlate with growth inhibition of prostate cancer cells treated in vitro with a novel anticancer drug, irofulven)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

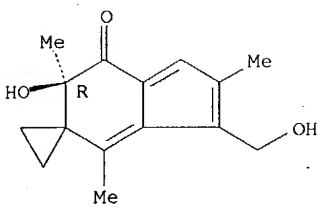
L5 ANSWER 31 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:696814 CAPLUS
DOCUMENT NUMBER: 136:65
TITLE: Ovarian cancer
AUTHOR(S): Seiden, Michael V.
CORPORATE SOURCE: Division of Hematology and Oncology, Massachusetts General Hospital, Boston, MA, 02114, USA
SOURCE: Oncologist (2001), 6(4), 327-332
CODEN: OCOLF6; ISSN: 1083-7159
PUBLISHER: AlphaMed Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. Ovarian cancer remains the most lethal gynecol. malignancy in women in the United States. Studies from this year's American Society of Clin. Oncol. more clearly defined the role of chemotherapy in women with early stage disease and now suggest that essentially all women with invasive disease should receive chemotherapy that contains carboplatin. Studies in women with advanced disease continue to support the use of carboplatin and paclitaxel in the treatment of women with newly diagnosed disease although early data suggest that carboplatin and docetaxel might be an acceptable alternative. Platinum-resistant disease remains a therapeutic challenge. Small mols. that inhibit the function of the epidermal growth factor receptor, such as OSI-774, and novel classes of chemotherapeutic agents, including the acylfulvene MGI-114 and epothilone B and its analog, BMS247550, all warrant further study in this disease.

IT **158440-71-2**, MGI-114
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ovarian cancer chemotherapy in humans)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



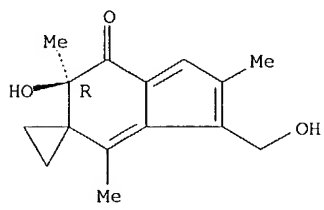
REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:623905 CAPLUS
DOCUMENT NUMBER: 136:318928
TITLE: Irofulven (6-hydroxymethylacylfulvene, MGI 114) induces caspase 8 and 9-mediated apoptosis in human pancreatic adenocarcinoma cells
AUTHOR(S): Wang, Weixin; Waters, Stephen J.; Macdonald, John R.; Von Hoff, Daniel D.; Strodel, William E.; Miller, Alexander R.
CORPORATE SOURCE: Department of Surgery, University of Texas Health Science Center at San Antonio, San Antonio, TX, 78229, USA
SOURCE: Anticancer Research (2001), 21(3B), 1789-1794
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background. Irofulven (MGI 114) is a novel, clin. active sesquiterpene whose mechanism of action is not fully understood. The authors sought to identify apoptotic effectors induced by this agent in human pancreatic cancer cells. Materials and Methods. MTT assay was used to assess IC50. Apoptosis was quantitated by flow cytometry and DAPI staining. Caspase activation was identified by Western blot anal. Results. Irofulven was cytotoxic against all pancreatic cancer cell lines tested (IC50 1-18 μM), and induced 10-fold (4% +/- 2, vs. 41% +/- 5) induction of apoptosis. Irofulven-treated cells also demonstrated PARP3 cleavage and DAPI staining. Apoptosis was reduced to baseline levels by Z-VAD-FMK, a broad-spectrum caspase inhibitor. Western blot anal. revealed that caspases-3, -7, -8, and -9 were activated by Irofulven. Time course evaluation demonstrated that caspases-8 and -9 were the initial species activated. Conclusion. Thus, the cytotoxicity of Irofulven in human pancreatic carcinoma cell lines is mediated by caspase-induced apoptosis.

IT **158440-71-2**, Irofulven
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Irofulven induces caspase 8 and 9-mediated apoptosis in human pancreatic adenocarcinoma cells)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



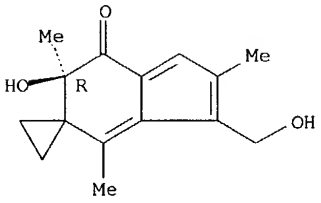
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 33 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:594861 CAPLUS
DOCUMENT NUMBER: 135:298185
TITLE: Structure-activity studies of antitumor agent irofulven (hydroxymethylacylfulvene) and analogues
AUTHOR(S): McMorris, Trevor C.; Yu, Jian; Lira, Ricardo; Dawe,

Robin; MacDonald, John R.; Waters, Stephen J.; Estes, Leita A.; Kelner, Michael J.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA, 92093-0506, USA
SOURCE: Journal of Organic Chemistry (2001), 66(18), 6158-6163
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:298185
AB Many analogs of the antitumor agent irofulven have been readily prepared by replacing the allylic hydroxyl with a variety of nucleophiles. Analogs of acylfulvene (the precursor to irofulven) were also prepared by Michael reaction with acrolein. The toxicity of the analogs was determined, as well as preclin. antitumor activity. Several analogs exhibited good activity in mouse xenografts. Structural requirements for activity are discussed.

IT **158440-71-2P**, Irofulven
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); RACT (Reactant or reagent); USES (Uses)
(antitumor activity of irofulven and its analogs)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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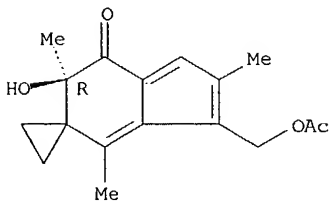
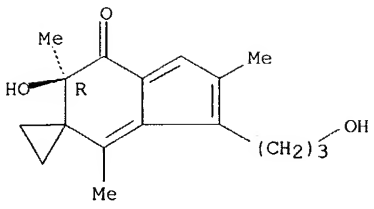
202799-34-6P 202799-46-0P 238432-47-8P
238432-55-8P 366615-81-8P 366615-87-4P
366615-93-2P 366616-08-2P 366616-14-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antitumor activity of irofulven and its analogs)
RN 168204-03-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(acetyloxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



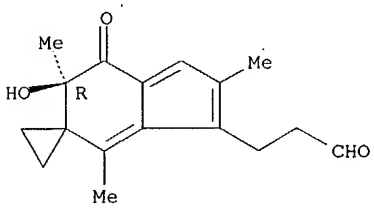
RN 202799-09-5 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(3-hydroxypropyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



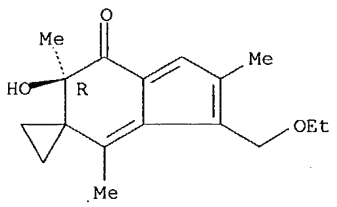
RN 202799-11-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]indene]-3'-propanal, 6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxo-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



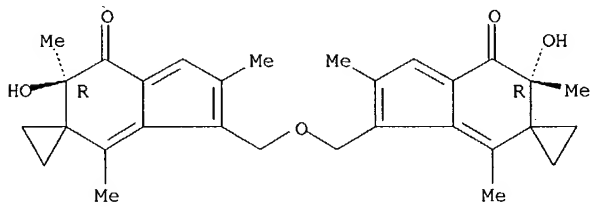
RN 202799-18-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-(ethoxymethyl)-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



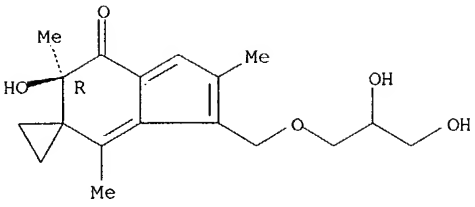
RN 202799-20-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-[oxybis(methylene)]bis[6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



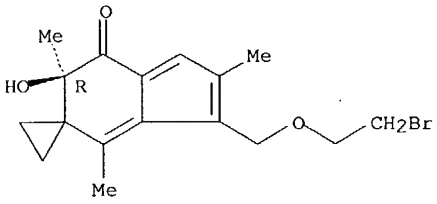
RN 202799-22-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(2,3-dihydroxypropoxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



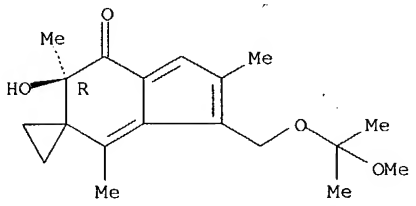
RN 202799-24-4 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(2-bromoethoxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



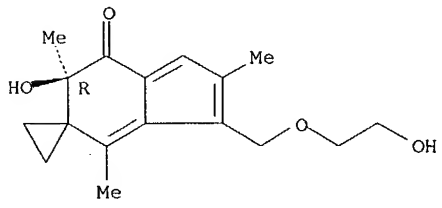
RN 202799-26-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(1-methoxy-1-methylethoxy)methyl]-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



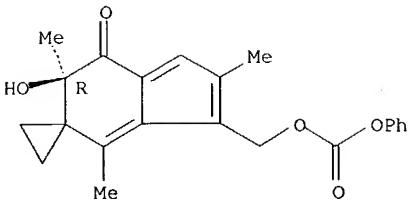
RN 202799-28-8 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(2-hydroxyethoxy)methyl]-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



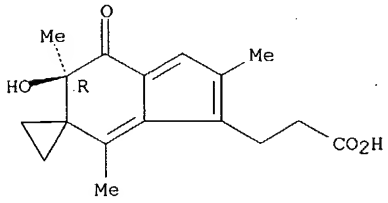
RN 202799-34-6 CAPLUS
CN Carbonic acid, [(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl phenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



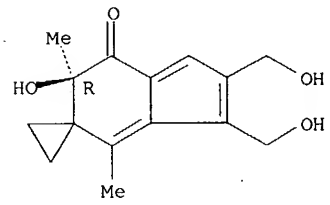
RN 202799-46-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]indene]-3'-propanoic acid, 6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxo-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



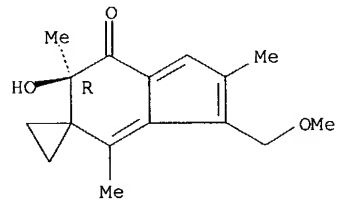
RN 238432-47-8 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',3'-bis(hydroxymethyl)-4',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



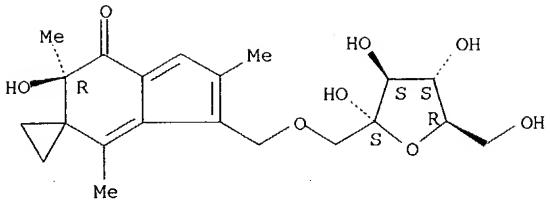
RN 238432-55-8 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(methoxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



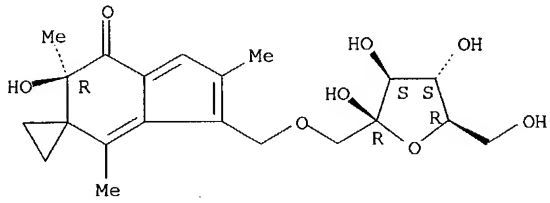
RN 366615-81-8 CAPLUS
CN α-D-Fructofuranose, 1-O-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



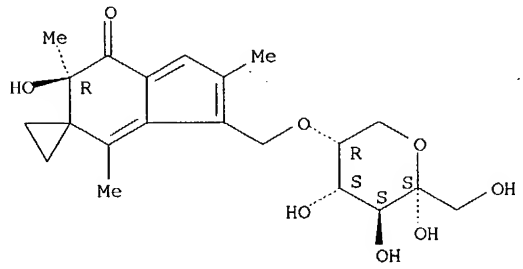
RN 366615-87-4 CAPLUS
CN β-D-Fructofuranose, 1-O-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



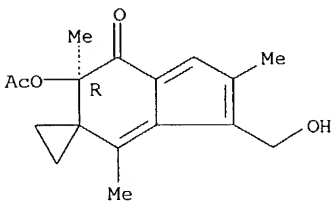
RN 366615-93-2 CAPLUS
CN α-D-Fructopyranose, 5-O-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



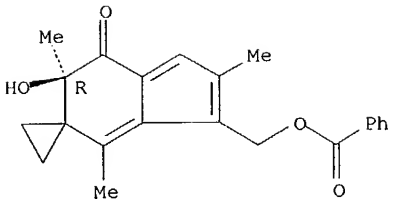
RN 366616-08-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-(acetyloxy)-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 366616-14-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(benzoyloxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



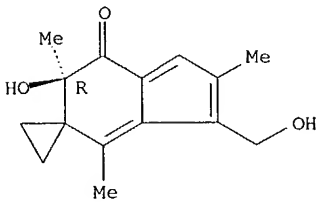
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 34 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:483139 CAPLUS
DOCUMENT NUMBER: 136:288614
TITLE: In vivo antitumor efficacy of MGI-114 (6-hydroxymethylacylfulvene, HMAF) in various human tumor xenograft models including several lung and gastric tumors
AUTHOR(S): Sato, Y.; Kashimoto, S.; MacDonald, J. R.; Nakano, K.
CORPORATE SOURCE: Discovery Research Laboratories, Department of Pharmacology II, Dainippon Pharmaceutical Co., Ltd., Suita, Osaka, 564-0053, Japan
SOURCE: European Journal of Cancer (2001), 37(11), 1419-1428
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The in vivo antitumor efficacy of MGI-114 (a semisynthetic analog of the cytotoxic sesquiterpenoid illudins) was examined in a panel of human tumor xenografts in mice, consisting mainly of human lung and gastric tumors, and compared with that of other antitumor drugs (irinotecan, paclitaxel, cisplatin, doxorubicin, vindesine, etoposide and 5-fluorouracil). When different administration schedules were compared, daily administration of MGI-114 was more effective than intermittent administrations. In human tumor xenograft models of nasopharyngeal, breast and colon carcinoma and melanoma, MGI-114 exerted a strong antitumor activity, with complete tumor regression occurring. Moreover, in four human lung and three gastric tumor xenografts, MGI-114 had a strong antitumor activity, with complete tumor regression occurring in some cases. The antitumor efficacy of MGI-114 was generally higher than or equivalent to that of irinotecan and paclitaxel. These results support the potential utility of MGI-114 in the treatment of a variety of human solid tumors.

IT **158440-71-2**, MGI 114
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor efficacy of MGI-114 (6-hydroxymethylacylfulvene) in various human tumor xenograft models)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

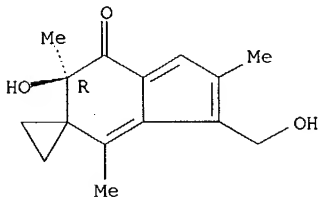


REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 35 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:258924 CAPLUS
DOCUMENT NUMBER: 135:220735
TITLE: A phase II trial of 6-hydroxymethylacylfulvene (MGI-114, irofulven) in patients with advanced non-small cell cancer previously treated with

chemotherapy
AUTHOR(S): Dowell, Jonathan E.; Johnson, David H.; Rogers, John S.; Shyr, Yu; McCullough, Nancy; Krozely, Peggy; De Vore, Russell F.
CORPORATE SOURCE: The Vanderbilt Clinic, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA
SOURCE: Investigational New Drugs (2001), 19(1), 85-88
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To test the efficacy and safety of the novel antitumor agent MGI-114 (NSC 683863) in patients with advanced non-small cell lung cancer (NSCLC) previously treated with chemotherapy. A two-stage accrual design was used to ensure detection of a true response rate of at least 20% with a type I error of .04. Eligible patients received 11 mg/m2 daily for five consecutive days. Cycles were repeated every 28 days. Fifteen patients received a total of 34 cycles of MGI-114. All patients had a performance status of 0 or 1. Eleven patients had previously received carboplatin and paclitaxel +/- radiation. Two patients had received cisplatin and CPT-11, one patient had received weekly paclitaxel, and one patient had received carboplatin and docetaxel. None of the first 15 patients enrolled experienced objective tumor response, and the study was closed. Forty percent of patients developed ≥ grade 2 thrombocytopenia. Grade 3 nausea and ≥ grade 2 vomiting were observed in 40% and 47% of patients resp. Thirty-three percent of patients experienced ≥ grade 2 fatigue. MGI-114, at this dose and schedule, does not have significant activity as second line therapy for patients with advanced NSCLC.
IT **158440-71-2**, NSC 683863
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(irofulven for treatment of patients with advanced non-small cell cancer previously treated with chemotherapy)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 36 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:258916 CAPLUS
DOCUMENT NUMBER: 135:189944
TITLE: Phase I study of irofulven (MGI 114), an acylfulvene illudin analog, in patients with acute leukemia
AUTHOR(S): Giles, Francis; Cortes, Jorge; Garcia-Manero, Guillermo; Kornblau, Stephen; Estey, Elihu; Kwari, Monica; Murgo, Anthony; Kantarjian, Hagop
CORPORATE SOURCE: Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
SOURCE: Investigational New Drugs (2001), 19(1), 13-20
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Irofulven (MGI 114, 6-hydroxymethylacylfulvene, HMAF) is a semisynthetic illudin analog with broad in vitro anti-neoplastic activity. In this leukemia phase I study, we investigated the toxicity profile and activity of Irofulven in patients with primary refractory or relapsed acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), or myelodysplastic syndromes (MDS). Irofulven was given as an i.v. infusion over five minutes daily for five days. The starting dose was 10 mg/m2/day (50

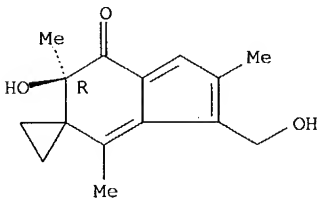
mg/m2/course). Courses were scheduled to be given every 3-4 wk according to toxicity and antileukemic efficacy. Twenty patients {AML: 17 patients; MDS: one patient; ALL: one patient; mixed lineage acute leukemia: one patient} were treated. Nausea, vomiting, hepatic dysfunction, weakness, renal dysfunction, and pulmonary edema were dose limiting toxicities, occurring in two of five patients treated at 20 mg/m2/day and two of three patients treated at 12.5 mg/m2/day. The MTD was defined as 10mg/m2/day for five days. One patient with primary resistant AML achieved complete remission. Proposed phase II studies will further define the activity of Irofulven in patients with better prognosis AML and in other hematol. malignancies, both as a single agent and in combination regimens, particularly with topoisomerase 1 inhibitors.

IT **158440-71-2,** Irofulven
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(phase I study of irofulven (MGI 114) in patients with acute leukemia)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 37 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2001:41340 CAPLUS

DOCUMENT NUMBER: 135:116637

TITLE: Phase I and pharmacokinetic study of irofulven, a novel mushroom-derived cytotoxin, administered for five consecutive days every four weeks in patients with advanced solid malignancies

AUTHOR(S): Eckhardt, S. Gail; Baker, Sharyn D.; Britten, Carolyn D.; Hidalgo, Manuel; Siu, Lillian; Hammond, Lisa A.; Villalona-Calero, Miguel A.; Felton, Sally; Drengler, Ronald; Kuhn, John G.; Clark, Gary M.; Smith, Sheri L.; MacDonald, John R.; Smith, Charlotte; Moczygemba, Judy; Weitman, Steve; Von Hoff, Daniel D.; Rowinsky, Eric K.

CORPORATE SOURCE: Institute for Drug Development, Cancer Therapy and Research Center, and Department of Medicine, Division of Oncology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

SOURCE: Journal of Clinical Oncology (2000), 18(24), 4086-4097
CODEN: JCONDN; ISSN: 0732-183X

PUBLISHER: Lippincott Williams & Wilkins

DOCUMENT TYPE: Journal

LANGUAGE: English

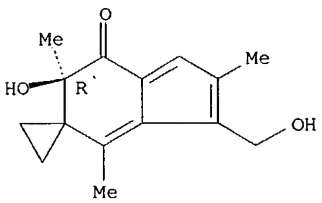
AB Aims of this study was to evaluate the toxicity and pharmacol. behavior of the novel mushroom-derived cytotoxin irofulven administered as a 5-min i.v. (IV) infusion daily for 5 days every 4 wk to patients with advanced solid malignancies. In this phase I trial, 46 patients were treated with irofulven doses ranging from 1.0 to 17.69 mg/m2 as a 5-min IV infusion (two patients received a 1-h infusion) daily for 5 days every 4 wk. The modified continual reassessment method was used for dose escalation. Pharmacokinetic studies were performed on days 1 and 5 to characterize the plasma disposition of irofulven. Forty-six patients were treated with 92 courses of irofulven. The dose-limiting toxicities on this schedule were myelosuppression and renal dysfunction. At the 14.15-mg/m2 dose level, renal dysfunction resembling renal tubular acidosis occurred in four of 10 patients and was ameliorated by prophylactic IV hydration. The 17.69-mg/m2 dose level was not tolerated because of grade 4 neutropenia and renal toxicity, whereas the 14.15-mg/m2 dose level was not tolerable with repetitive dosing because of persistent thrombocytopenia. Other

common toxicities included mild to moderate nausea, vomiting, facial erythema, and fatigue. One partial response occurred in a patient with advanced, refractory metastatic pancreatic cancer lasting 7 mo. Pharmacokinetic studies of irofulven revealed dose-proportional increases in both maximum plasma concns. and area under the concentration-time curve, while the agent exhibited a rapid elimination half-life of 2 to 10 min. Given the results of this study, the recommended dose of irofulven is 10.64 mg/m2 as a 5-min IV infusion daily for 5 days every 4 wk. The preliminary antitumor activity documented in a patient with advanced pancreatic cancer and the striking preclin. antitumor effects of irofulven observed on intermittent dosing schedules support further disease-directed evaluations of this agent on the schedule evaluated in this study.

IT **158440-71-2**, Irofulven
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(toxicity and pharmacokinetic of irofulven, a novel mushroom-derived cytotoxin, administered for five consecutive days every four weeks in humans with advanced solid malignancies)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

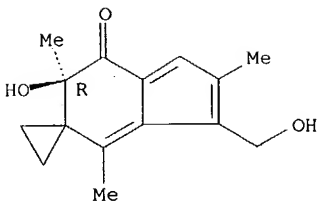
L5 ANSWER 38 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:846297 CAPLUS
DOCUMENT NUMBER: 136:275422
TITLE: Targeting apoptosis by hydroxymethylacylfulvene in combination with gamma radiation in prostate tumor cells. [Erratum to document cited in CA134:14785]
AUTHOR(S): Woynarowska, Barbara A.; Roberts, Kari; Woynarowski, Jan M.; MacDonald, John R.; Herman, Terence S.; Moyer, Mary Pat
CORPORATE SOURCE: Department of Radiation Oncology, University of Texas Health Science Center, San Antonio, TX, 78284, USA
SOURCE: Radiation Research (2000), 154(5), 608, 8
CODEN: RAREAE; ISSN: 0033-7587
PUBLISHER: Radiation Research Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB One author, Mary Pat Moyer, was omitted from the list of authors; she is affiliated with INCELL Corporation, LLC, San Antonio, Texas 78249.

IT **158440-71-2**, MGI 114
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting apoptosis by hydroxymethylacylfulvene and γ-irradiation in prostate tumor (Erratum))

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



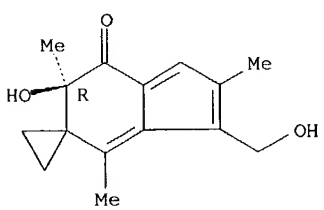
L5 ANSWER 39 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:834318 CAPLUS
DOCUMENT NUMBER: 135:55558
TITLE: Enhanced antitumour activity of 6-hydroxymethylacylfulvene in combination with topotecan or paclitaxel in the MV522 lung carcinoma xenograft model
AUTHOR(S): Hammond, L. A.; Hilsenbeck, S. G.; Eckhardt, S. G.; Marty, J.; Mangold, G.; MacDonald, J. R.; Rowinsky, E. K.; Von Hoff, D. D.; Weitman, S.
CORPORATE SOURCE: Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, TX, 78245-3217, USA
SOURCE: European Journal of Cancer (2000), 36(18), 2430-2436
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 6-Hydroxymethylacylfulvene (HMAF; MGI 114; Irofulven) is a semisynthetic analog of the toxin illudin S, which is a product of the Omphalotus mushroom. MGI 114 induces cytotoxicity against a broad range of solid tumors in vivo, including the drug-refractory MV522 human lung cancer xenograft. In this study, the potential application of MGI 114 in the treatment of lung cancer was explored by evaluating the activity of MGI 114 in combination with either topotecan (TPT) or paclitaxel. Groups of eight nude mice bearing MV522 xenografts were treated with MGI 114, TPT or paclitaxel as single agents and with MGI 114 in combination with TPT or paclitaxel. MGI 114 was administered at doses of 2.5 and 5.0 mg/kg i.p. (i.p.) daily on days 1-5, while TPT and paclitaxel were administered at doses of 0.5 or 1.0 mg/kg and 20 mg/kg, resp., i.p. on days 1-5. In the single-agent studies, MGI 114, TPT and paclitaxel all resulted in decreased final tumor wts. compared with vehicle-treated controls. As single agents, TPT, at the 0.5 mg/kg dose level, and paclitaxel, at the 20 mg/kg dose level, produced partial shrinkages (PSs). All combinations of MGI 114, and either TPT or paclitaxel, produced decrements in final tumor wts. compared with monotherapy with the same doses of MGI 114, TPT and paclitaxel. Although all animals treated with the combination of MGI 114 and paclitaxel experienced PSs or complete shrinkages (CSs) (or died), anal. of the time to tumor doubling revealed that the combination of MGI 114 and TPT at 2.5 and 0.5 mg/kg, resp., was synergistic. These results suggest that cytotoxic activity is enhanced when MGI 114 is combined with either TPT or paclitaxel, and clin. trials to further evaluate these combination regimens are warranted.

IT **158440-71-2**, Irofulven
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced antitumor activity of 6-hydroxymethylacylfulvene in combination with topotecan or paclitaxel in MV522 lung carcinoma xenograft model)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



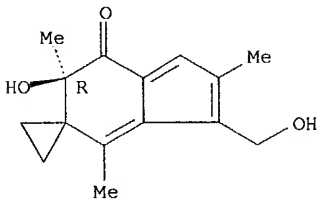
REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 40 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:727953 CAPLUS
DOCUMENT NUMBER: 134:14785
TITLE: Targeting apoptosis by hydroxymethylacylfulvene in combination with gamma radiation in prostate tumor cells
AUTHOR(S): Woynarowska, Barbara A.; Roberts, Kari; Woynarowski, Jan M.; MacDonald, John R.; Herman, Terence S.
CORPORATE SOURCE: Department of Radiation Oncology, University of Texas Health Science Center, San Antonio, TX, 78284, USA
SOURCE: Radiation Research (2000), 154(4), 429-438
CODEN: RAREAE; ISSN: 0033-7587
PUBLISHER: Radiation Research Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hydroxymethylacylfulvene (HMAF) is a novel agent with alkylating activity and is a potent inducer of apoptosis that is currently undergoing Phase II clin. trials for prostate cancer. This study explored the pro-apoptosis and anti-proliferative potential of HMAF in combination with γ radiation in human prostate tumor cell lines. Apoptosis was assessed based on the generation of fragmented DNA, a terminal transferase flow cytometry assay, and cell morphol. In each of the tumor cell lines examined, radiation alone induced a marginal level of apoptosis, even after a prolonged 48-h incubation after exposure. In contrast, HMAF alone was a potent inducer of apoptosis in prostate tumor cells but not in normal cells. Marked levels of apoptosis in tumor cells were also observed for the combination of HMAF with γ radiation. When drug treatment preceded irradiation, at least additive levels of apoptosis were observed in both androgen-responsive and androgen-independent cells. The combined treatment with ionizing radiation and HMAF reduced the radiation dose needed for the same level of clonogenic survival up to 2.5-fold. The potentiation of apoptosis and reduction in the clonogenic survival of tumor cells occurred at HMAF concns. lower than that which reduced survival to 10% and at doses up to 6 Gy. No potentiation of apoptosis or clonogenic inhibition was noted in normal cells. These results suggest that the combination of HMAF with γ radiation may have clin. utility for treatments of prostate cancer.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(targeting apoptosis by hydroxymethylacylfulvene and γ-irradiation in prostate tumor)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 41 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:612956 CAPLUS
DOCUMENT NUMBER: 133:335446
TITLE: Preparation and biological activity of amino acid and peptide conjugates of antitumor hydroxymethylacylfulvene
AUTHOR(S): McMorris, Trevor C.; Yu, Jian; Ngo, Huan-Tony; Wang, Haixia; Kelner, Michael J.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, La Jolla, CA, 92093-0506, USA

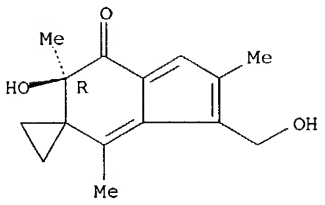
SOURCE: Journal of Medicinal Chemistry (2000), 43(19), 3577-3580
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The primary hydroxy group in hydroxymethylacylfulvene, a potent antitumor drug, is readily replaced by thiols from cysteine, N-acetylcysteine, homocysteine and glutathione. Best yields are obtained when reaction is carried out in the presence of dilute sulfuric acid. A variety of sulfur-containing analogs, such as I [X = OH, NHCH(Me)Ph] and peptide derivs. I [X = -Phe-Gly-Leu-OH, -Leu-Gly-Phe-OH, -Leu-Leu-Phe-OH and -(Leu)3-OH], have been prepared and their toxicity to tumor cells was examined

IT **158440-71-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation and antitumor activity of amino acid and peptide conjugates of hydroxymethylacylfulvene)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

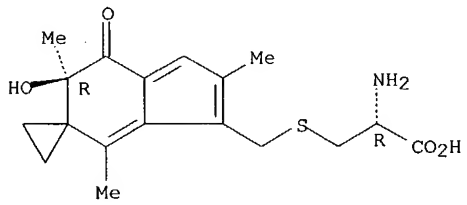
Absolute stereochemistry.



IT **202799-44-8P 238432-56-9P 238432-57-0P**
238432-58-1P 238432-59-2P 303956-62-9P
303956-63-0P 303956-64-1P 303956-65-2P
303956-66-3P 303956-67-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of amino acid and peptide conjugates of hydroxymethylacylfulvene)

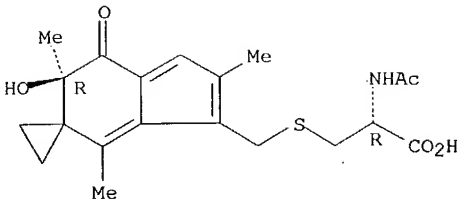
RN 202799-44-8 CAPLUS
CN L-Cysteine, S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



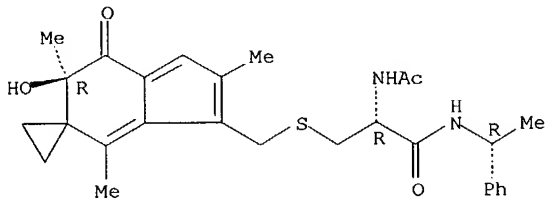
RN 238432-56-9 CAPLUS
CN L-Cysteine, N-acetyl-S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



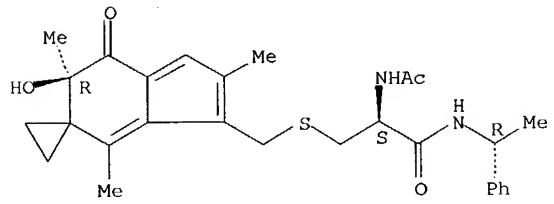
RN 238432-57-0 CAPLUS
CN Propanamide, 2-(acetylamino)-3-[[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]thio]-N-[(1R)-1-phenylethyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



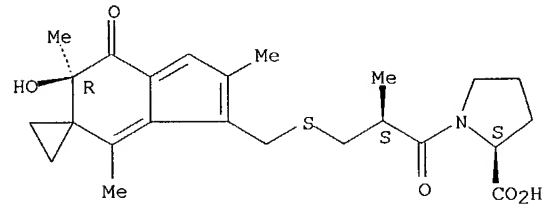
RN 238432-58-1 CAPLUS
CN Propanamide, 2-(acetylamino)-3-[[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]thio]-N-[(1R)-1-phenylethyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



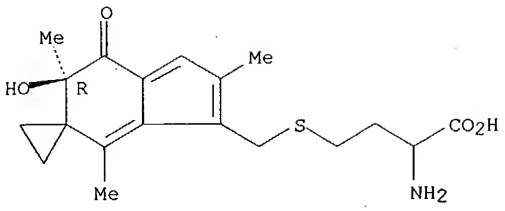
RN 238432-59-2 CAPLUS
CN L-Proline, 1-[(2S)-3-[[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]thio]-2-methyl-1-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



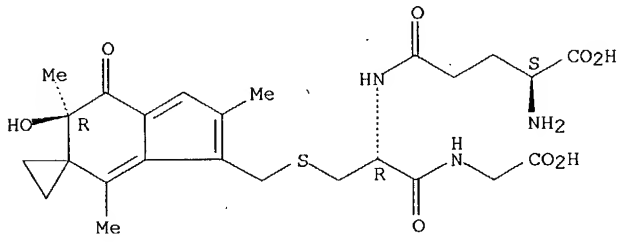
RN 303956-62-9 CAPLUS
CN Homocysteine, S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



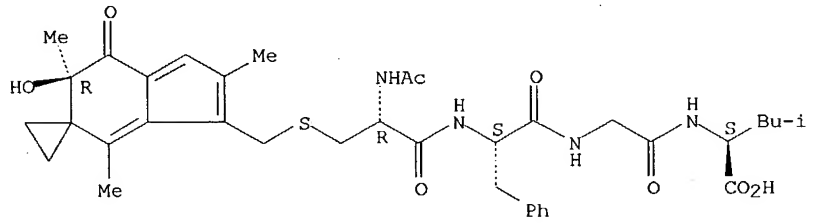
RN 303956-63-0 CAPLUS
CN Glycine, L-γ-glutamyl-S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



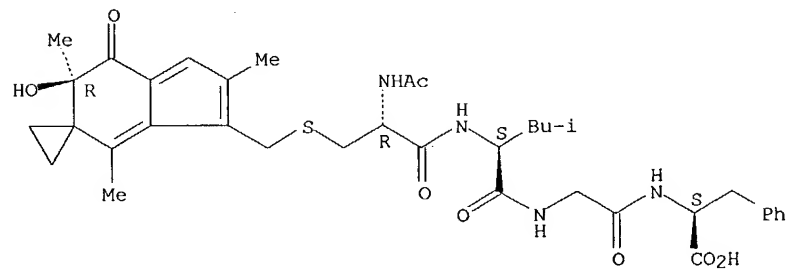
RN 303956-64-1 CAPLUS
CN L-Leucine, N-acetyl-S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]-L-cysteinyl-L-phenylalanylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



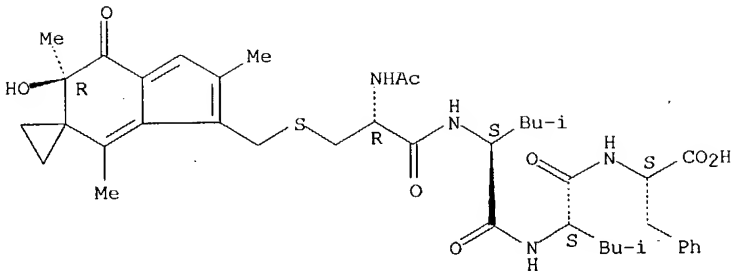
RN 303956-65-2 CAPLUS
CN L-Phenylalanine, N-acetyl-S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]-L-cysteinyl-L-leucylglycyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



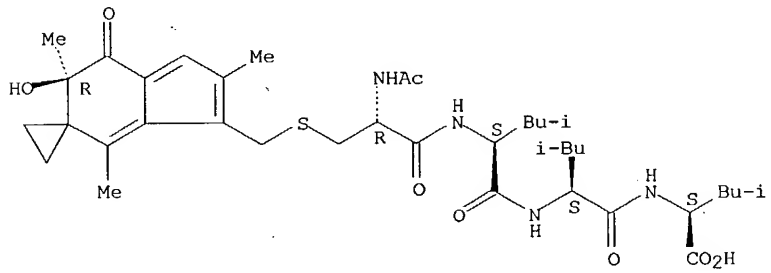
RN 303956-66-3 CAPLUS
CN L-Phenylalanine, N-acetyl-S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]-L-cysteinyl-L-leucyl-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 303956-67-4 CAPLUS
CN L-Leucine, N-acetyl-S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]-L-cysteinyl-L-leucyl-L-leucyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



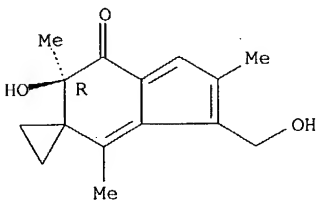
REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 42 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:336037 CAPLUS
DOCUMENT NUMBER: 133:83997
TITLE: Efficacy of MGI 114 (HMAF) against the MRP+ metastatic MV522 lung carcinoma xenograft
AUTHOR(S): Kelner, Michael J.; McMorris, Trevor C.; Estes, Leita A.; Oval, Michelle Y.; Rojas, Rafael J.; Lynn, Joshua R.; Lanham, Kevin A.; Samson, Kyra M.
CORPORATE SOURCE: Department of Pathology, University of California, San Diego, La Jolla, CA, 92093, USA
SOURCE: Anti-Cancer Drugs (2000), 11(3), 217-224
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB This study is part of an effort to evaluate efficacy of the novel agent MGI 114 (HMAF) against tumors resistant to conventional chemotherapeutic agents. MGI 114 is a novel semisynthetic anticancer agent currently in chemotherapeutic phase II trials to evaluate activity against various solid tumors. Previous studies indicate MGI 114 was active against human MDR1/gp170+ solid tumor xenografts. Recent evidence suggests overexpression of the MRP protein may also be clin. relevant to development of drug resistance in solid tumors. We evaluated the efficacy of MGI 114 against a human MRP+ lung carcinoma xenograft. Parent MV522 lung carcinoma cells were transfected with a MRP cDNA expression vector and resistant cells selected by exposure to vinblastine (30-fold resistance). Anal. of resistant clones indicated 20- to 40-fold increases in expression of both MRP mRNA and MRP protein. Administration of MGI 114 at the maximum tolerated dose (7 mg/kg, 5 + /wk for 3 wk) to MRP tumor-bearing mice demonstrated this novel agent was active against MRP+ tumors and significantly extended their lifespan ($p<0.001$). In contrast, other cytotoxic agents had minimal activity against this MRP+ xenograft. These results indicate MGI 114 should retain activity in vivo against MRP+ tumor types. The development of this MRP+ xenograft model, in conjunction with the parent MV522 and MDR1/gp170+ xenograft models, will be useful for screening new classes of agents for activity against multidrug-resistant tumors.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of MGI 114 (HMAF) against MRP+ metastatic MV522 lung carcinoma xenograft)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

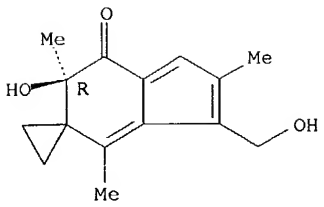
Absolute stereochemistry.



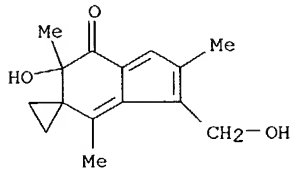
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 43 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:285952 CAPLUS
DOCUMENT NUMBER: 133:105171
TITLE: A Rapid Synthesis of Hydroxymethylacylfulvene (HMAF) Using the Allenic Pauson-Khand Reaction. A Synthetic Approach to Either Enantiomer of This Illudane Structure
AUTHOR(S): Brummond, Kay M.; Lu, Jianliang; Petersen, Jeffrey
CORPORATE SOURCE: Department of Chemistry, West Virginia University, Morgantown, WV, 26506-6045, USA
SOURCE: Journal of the American Chemical Society (2000), 122(20), 4915-4920
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:105171
AB An allenic Pauson-Khand reaction has been employed in the preparation of (±)-hydroxymethylacylfulvene (HMAF) I, an anticancer agent that is currently in Phase II clin. trials for a variety of solid tumor types. The synthesis of I is effected in 11 steps from com. available starting materials. In addition, an asym. route to HMAF has been established by the preparation of a single enantiomer II (TBS = Me3CSiMe2) of an intermediate in the preparation of HMAF. The key step in the preparation of II was the Sharpless asym. dihydroxylation (AD) of the trisubstituted olefin in enyne III (RR1 = O) to give diol IV (R2 = Me3Si) in 49% yield and >95% ee in addition to the terminally desilylated IV (R2 = H) in 11% yield and >95% ee; silylation of IV (R2 = Me3Si) gave enantiomerically pure II in 76% yield. This approach provides access to both enantiomers of HMAF simply by changing the ligands in the Sharpless AD reaction. Optimized conditions for the stereospecific synthesis of E or Z trisubstituted enynes from an aliphatic ketone using either Peterson olefination or Horner-Wadsworth-Emmons protocols are reported. Peterson olefination of diacetylcyclopropane ketal V with Me3SiC.tplbond.CCH2SiMe3 gave the Z stereoisomer of enyne III (RR1 = OCH2CH2O) in 42% yield as a single isomer if the temperature was carefully controlled; the (E)-enyne III (RR1 = OCH2CH2O) was prepared in 86% yield as a single stereoisomer by olefination of V with Me3SiC.tplbond.CCH2P(:O)(OEt)2 with NaN(SiMe3)2 as the base. Finally, a better understanding of the stereoelectronic requirements of the allenic P-K reaction is recognized.
IT **158440-71-2P 187277-46-9P**, (±)-Hydroxymethylacylfulvene **283168-03-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of racemic hydroxymethylacylfulvene and a formal synthesis of its enantiomers by a Pauson-Khand cyclization of an allenic enyne)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

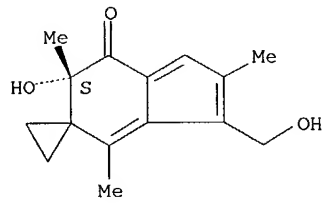


RN 187277-46-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl- (9CI) (CA INDEX NAME)



RN 283168-03-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

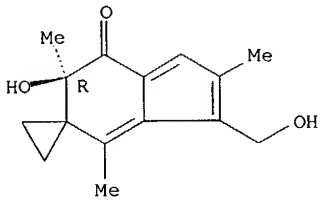
L5 ANSWER 44 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:200997 CAPLUS
DOCUMENT NUMBER: 133:99179
TITLE: Differential cytotoxicity and induction of apoptosis in tumor and normal cells by hydroxymethylacylfulvene (HMAF)
AUTHOR(S): Woynarowska, B. A.; Woynarowski, J. M.; Herzig, M. C. S.; Roberts, K.; Higdon, A. L.; MacDonald, J. R.
CORPORATE SOURCE: The University of Texas Health Science Center, San Antonio, TX, USA
SOURCE: Biochemical Pharmacology (2000), 59(10), 1217-1226
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This investigation compared the effects of hydroxymethylacylfulvene (HMAF), a novel antitumor drug with alkylating properties, in eight human tumor (prostate, colon, and leukemia) cell lines, and five human normal (prostate and renal proximal tubule epithelial, colon mucosa, fibroblasts, and endothelial) cell lines. Drug-induced growth inhibition paralleled the uptake of HMAF into both tumor and normal cells, although normal cells were 3- to 4-fold more tolerant to the accumulated drug. In both tumor and normal cells, approx. two-thirds of internalized [14C]HMAF-derived radioactivity was bound covalently to macromols. Trypan blue exclusion and cell counts indicated that HMAF was cytotoxic in tumor but cytostatic in normal cells. Correspondingly, profound apoptosis was detected in all tumor cell lines examined A 4-h treatment with HMAF followed by 20-h post-incubation induced a potent DNA fragmentation in nearly all tumor lines. Apoptosis-resistant PC-3 and HT-29 cells underwent significant DNA

fragmentation after 24 h of continuous treatment with HMAF. In contrast to tumor cell lines, marginal or very low levels of apoptosis were detected in the normal cells even after prolonged treatments with HMAF at concns. that exceeded 15- to 800-fold the GI50 values in tumor cells. This resistance of normal cells to apoptosis could not be accounted for by differences in drug accumulation or drug covalent binding to macromols. The qual. different responses of the tumor and normal cells studied suggest a greater tolerance of normal cells to HMAF-macromol. adducts. The demonstrated differential cytotoxic/cytostatic and apoptotic effects of HMAF can be of significance for the clin. use of this promising new agent.

IT **158440-71-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(differential cytotoxicity and induction of apoptosis in tumor and normal cells by hydroxymethylacylfulvene)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 45 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:180511 CAPLUS
DOCUMENT NUMBER: 133:232495
TITLE: Evaluation of antidotes for extravasation injury produced by 6-hydroxymethylacylfulvene (MGI 114), a novel cytotoxic antitumor agent, in an intradermal toxicity model in rats
AUTHOR(S): Marshall, Richard F.; Arthaud, Larry E.; MacDonald, John R.
CORPORATE SOURCE: MGI Pharma, Inc., Bloomington, MN, 55348-2318, USA
SOURCE: Cancer Chemotherapy and Pharmacology (2000), 45(5), 397-401
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The degree of soft tissue injury produced by MGI 114 after intradermal administration to rats was quantified and 4 potential antidotes for extravasation injuries caused by MGI 114 were evaluated. Intradermal injections of MGI 114 (0.2 mL, 0.1, 0.5 or 1.0 mg/mL) and a pos. control, doxorubicin (0.2 mL, 2 mg/mL) were administered to male Fischer 344 rats. Dermal lesions at the injection sites were measured and quantitated as the total area under the lesion area-time curve (AUC). Physiol. saline, sodium thiosulfate, DMSO and local cooling were then compared as potential antidotes in this model. Dermal lesions (erythema, ulcerations and eschar formation) occurred at the MGI 114- and doxorubicin-treated sites. The lesion area resulting from MGI 114 was dose-related and was greatest after approx. 5 days, with resolution by day 7-22. Doxorubicin-induced lesions were comparable in area to those induced by the highest dose of MGI 114, but persisted approx. twice as long. In the antidote study with MGI 114, sodium thiosulfate administration resulted in approx. 20% diminution of lesion area and AUC value when compared to untreated controls. Normal saline caused slight redns. in maximum lesion area, but had little effect on AUC values. Local cooling also caused a modest reduction in the maximum lesion area, but actually resulted in higher AUC values by prolonging eschar duration. DMSO provided nearly complete tissue protection from intradermal exposure to MGI 114. MGI 114 and doxorubicin produced similar soft tissue injuries, but MGI 114-induced lesions tended to show a more rapid resolution Topical DMSO treatment produced the most effective

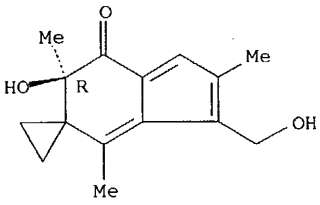
protection against MGI 114-induced local tissue irritation and necrosis.

IT **158440-71-2**, MGI 114
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(antidotes for extravasation injury produced by MGI 114)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 46 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 2000:109470 CAPLUS

DOCUMENT NUMBER: 133:26491

TITLE: Antileukemic action of the novel agent MGI 114 (HMAF) and synergistic action with topotecan

AUTHOR(S): Kelner, M. J.; McMorris, T. C.; Estes, L.; Samson, K. M.; Trani, N. A.; MacDonald, J. R.

CORPORATE SOURCE: Department of Pathology, University of California, San Diego, CA, USA

SOURCE: Leukemia (2000), 14(1), 136-141
CODEN: LEUKED; ISSN: 0887-6924

PUBLISHER: Nature Publishing Group

DOCUMENT TYPE: Journal

LANGUAGE: English

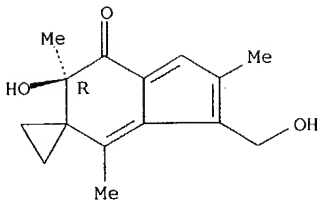
AB The illudin derivative MGI 114 (6-hydroxymethylacylfulvene, HMAF) is currently in phase II chemotherapeutic clin. trials for a variety of solid tumors. The illudins were originally thought to be potentially useful agents for myeloid leukemias, because hematopoietic tumor cells were markedly sensitive, whereas normal bone marrow progenitors were relatively resistant to the cytotoxic effects of illudins. The present studies were undertaken to evaluate the efficacy of MGI 114 in the HL60/MRI myeloid leukemia xenograft in mice. In addition, because of the reported synergistic cytotoxic activity between MGI 114 and the topoisomerase I inhibitor topotecan towards pediatric human tumor cell lines, the activity of MGI 114 and topotecan combinations was tested against HL60 cells in vitro and the HL60/MRI myelocytic xenograft. MGI 114 at maximum tolerated doses (MTD) of 7 mg/kg, 5 times/wk for 3 wk, displayed antimyeloid leukemic properties in the HL60/MRI xenograft model, an effect which exceeds the activity previously noted with other conventional agents. A marked therapeutic synergistic action was observed with MGI 114 and topotecan combinations, with a 50% MTD of each agent producing complete tumor remission in 50% of the animals, without development of excessive or additive toxicity. These results support further in vitro and clin. investigation into both the antimyeloid leukemic activity of MGI-114, and the cooperative pharmacol. interaction noted between MGI-114 and topoisomerase I inhibitors.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antileukemic action of the illudin derivative MGI 114 (HMAF) and its synergistic action with topotecan)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

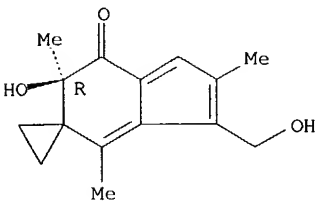
L5 ANSWER 47 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:809619 CAPLUS
DOCUMENT NUMBER: 132:117242
TITLE: Antitumor activity of MGI 114 (6-hydroxymethylacylfulvene, HMAF), a semisynthetic derivative of illudin S, against adult and pediatric human tumor colony-forming units
AUTHOR(S): Hidalgo, Manuel; Izbicka, Elzbieta; Eckhardt, S. Gail; MacDonald, John R.; Cerna, Cesario; Gomez, Lionel; Rowinsky, Eric K.; Weitman, Steven D.; Von Hoff, Daniel D.
CORPORATE SOURCE: Institute for Drug Development, Cancer Therapy and Research Center, University of Texas Health Science Center at San Antonio, San Antonio, TX, 78229, USA
SOURCE: Anti-Cancer Drugs (1999), 10(9), 837-844
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MGI 114 (6-hydroxymethylacylfulvene, HMAF) is a novel semisynthetic antitumor compound derived from the sesquiterpene mushroom toxin illudin S. Although illudins did not demonstrate significant activity as antiproliferative agents in tumor-bearing animals, several properties including its potent inhibition of DNA synthesis and a unique interaction with DNA led to a structure-activity-based synthetic effort to obtain analogs with improved therapeutic potential. MGI 114 was selected for further development based on its antitumor activity in numerous preclin. tests. MGI 114 was evaluated against adult and pediatric human tumors taken directly from cancer patients and cultured in a human tumor colony-forming assay (HTCFA) to assess the antitumor spectra, concentration-response relationship, schedule dependence and activity of this agent against tumors considered resistant to conventional anticancer drugs. Human tumor colony-forming units were treated with HMAF at concns. of 0.001, 0.01, 0.1 and 1 μg/mL, both as a 1 h exposure and as a continuous 14 day exposure. A response was scored if there was 50% or less colony survival. In vitro response rates in the range of 50-80% were observed against tumor colony-forming units originating from carcinomas of the colon, kidney, breast, lung cancer, ovary and melanoma. MGI 114 also demonstrated antitumor activity against neuroblastoma colony-forming units. Antitumor activity was not influenced by exposure time as demonstrated by the similar responses rates obtained with the 1 h and continuous exposure at all concns. tested. However, there was a significant pos. concentration-response relationship to both exposure duration with responses increasing from below 10% at the lowest concentration to over 70% at the highest concentration, except for the pediatric tumors on the 1 h exposure for which this relationship was less apparent. At the higher concentration tested, MGI 114 displayed substantial antiproliferative effects in the range of 70% against tumor specimens resistant to classic cytotoxic agents including irinotecan, paclitaxel, 5-fluorouracil, cisplatin, doxorubicin and cyclophosphamide. These results demonstrate that MGI 114 exhibits a broad spectrum of antitumor activity against both adult and pediatric primary tumor colony-forming units in a concentration-dependent manner both at short and prolonged exposure duration. The substantial in vitro activity of MGI 114 at concns. achievable in clin. trials, together with its activity against tumors resistant to classic standard cytotoxic drugs, justifies the further clin. evaluation of this unique agent.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of MGI 114 against adult and pediatric human tumor colony-forming units)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

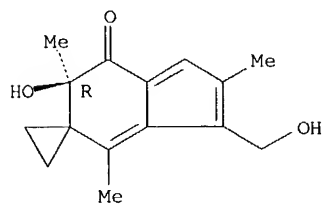
L5 ANSWER 48 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:574895 CAPLUS
DOCUMENT NUMBER: 131:306712
TITLE: Metabolism of antitumor hydroxymethylacylfulvene by rat liver cytosol
AUTHOR(S): Mcmorris, Trevor C.; Elayadi, Anissa N.; Yu, Jian; Hu, Yi; Kelner, Michael J.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, La Jolla, CA, 92093-0506, USA
SOURCE: Drug Metabolism and Disposition (1999), 27(9), 983-985
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Acylfulvenes are a potent class of antitumor agents derived from illudin S, a fungal sesquiterpene. Illudin S possesses antitumor activity but has a poor therapeutic index. Acylfulvene is 100-fold less toxic against human lung adenocarcinoma cells than illudin S, but inhibits tumor growth in human xenografts, opposite to illudin S. An analog of acylfulvene, MGI 114 (hydroxymethylacylfulvene), shows much greater efficacy, producing complete tumor regression in xenograft models. MGI 114 is currently in phase II clin. trials. Cytotoxicity of MGI 114, like that of illudin S, is believed to involve both chemical reaction and enzymic reduction Enzymic reduction by a cytosolic NADPH-dependent enzyme (from rat liver) produced an aromatic metabolite similar to that formed from illudin S. However, the reaction occurred more slowly. In addition, four new metabolites were isolated, two hydroxylated derivs. and two in which the primary allylic hydroxyl was replaced by hydride. All retained the reactive centers of the parent MGI 114.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(liver metabolism of antitumor drug MGI 114 (hydroxymethylacylfulvene))

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

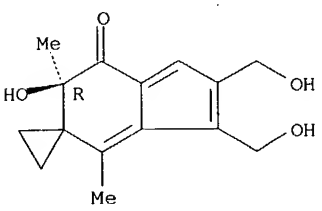


IT **238432-47-8 247256-78-6 247256-79-7 247256-80-0**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative)

(liver metabolism of antitumor drug MGI 114 (hydroxymethylacylfulvene))

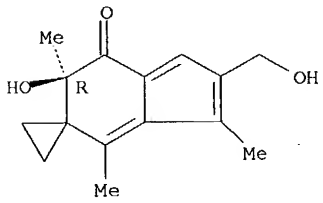
RN 238432-47-8 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',3'-bis(hydroxymethyl)-4',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



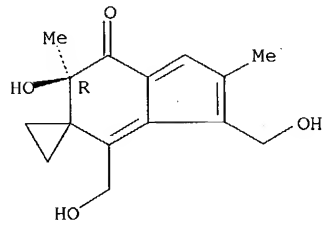
RN 247256-78-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2'-(hydroxymethyl)-3',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



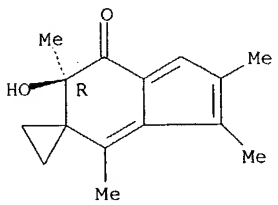
RN 247256-79-7 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3',4'-bis(hydroxymethyl)-2',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 247256-80-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',3',4',6'-tetramethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 49 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:549241 CAPLUS
DOCUMENT NUMBER: 131:170635

TITLE: Preparation of spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one derivatives as antitumor agents

INVENTOR(S): McMorris, Trevor C.; Kelner, Michael J.

PATENT ASSIGNEE(S): The Regents of the University of California, USA

SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9942429	A1	19990826	WO 1999-US3660	19990219
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6025328	A	20000215	US 1998-26633	19980220
CA 2321149	AA	19990826	CA 1999-2321149	19990219
AU 9926886	A1	19990906	AU 1999-26886	19990219
AU 764375	B2	20030814		
BR 9908125	A	20001024	BR 1999-8125	19990219
EP 1056704	A1	20001206	EP 1999-907161	19990219
EP 1056704	B1	20030502		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200002418	T2	20010122	TR 2000-200002418	19990219
EE 200000472	A	20011217	EE 2000-472	19990219
JP 2002503714	T2	20020205	JP 2000-532383	19990219
AT 238981	E	20030515	AT 1999-907161	19990219
NZ 506592	A	20030725	NZ 1999-506592	19990219
PT 1056704	T	20030829	PT 1999-907161	19990219
ES 2199551	T3	20040216	ES 1999-907161	19990219
US 6323181	B1	20011127	US 1999-386555	19990831
US 6548679	B1	20030415	US 2000-641191	20000817
NO 2000004162	A	20001018	NO 2000-4162	20000818
HK 1033574	A1	20040319	HK 2001-103838	20010604
US 2002086815	A1	20020704	US 2001-13009	20011105
US 2004034202	A1	20040219	US 2003-413449	20030414

PRIORITY APPLN. INFO.:

US 1998-26633	A2	19980220
WO 1999-US3660	W	19990219
US 1999-386555	A1	19990831
US 2000-641191	A1	20000817

OTHER SOURCE(S): MARPAT 131:170635

AB Title spiro compds. I [R1 = H, OH, SH, NH2, halo, CO2H, NO2, or (CH2)n-X-Y, where n = 0-4, X = O, S, NRa (Ra = H, alkyl, alkanoyl, Ph, or benzyl), or absent; Y = cycloalkyl, aryl, heteroaryl, a saccharide, an amino acid, a peptide, (un)substituted carbon chain having, O, S, NRa groups; R2 = CO2H, alkanoyl, alkoxycarbonyl, haloalkyl, carboxamido, a saccharide, an amino acid, a peptide, (un)substituted alkyl; R3 = H, alkyl, alkoxy, alkylthio, aryl, heteroaryl, aryloxy, heteroaryloxy; R4 = H, alkyl; R5 = OH, alkoxy, alkanoyloxy; or R4R5 = ethylenedioxy; R6 = H, CO2H, alkanoyl, alkoxycarbonyl, haloalkyl, carboxamido, a saccharide, an amino acid, a peptide, (un)substituted alkyl] and related spirocyclopropaneindenediones or their pharmaceutically acceptable salts were prepared as antitumor agents. Thus, compound II, prepared by reaction of HMAF with N-acetylcysteine, showed IC50 10,000 ± 1,800 nm/l against MV522 (human lung carcinoma cell line).

IT **168204-03-3P 238432-47-8P 238432-49-0P 238432-53-6P 238432-55-8P 238432-56-9P**

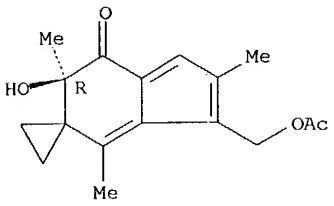
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(preparation of spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one derivs. and their amino acid derivs. as antitumor agents)

RN 168204-03-3 CAPLUS

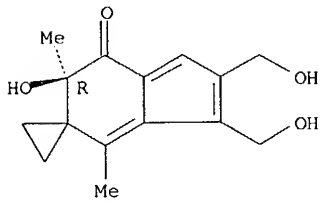
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(acetyloxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



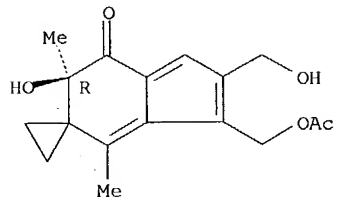
RN 238432-47-8 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',3'-bis(hydroxymethyl)-4',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



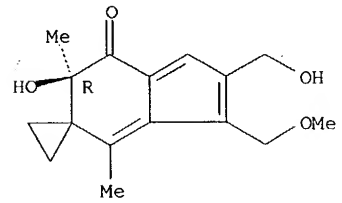
RN 238432-49-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(acetyloxy)methyl]-6'-hydroxy-2'-(hydroxymethyl)-4',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



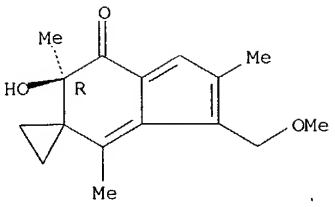
RN 238432-53-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2'-(hydroxymethyl)-3'-(methoxymethyl)-4',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



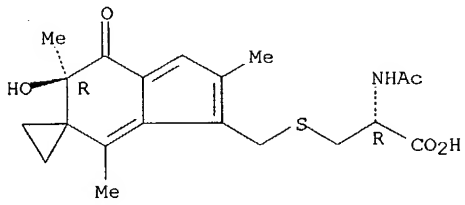
RN 238432-55-8 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(methoxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 238432-56-9 CAPLUS
CN L-Cysteine, N-acetyl-S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

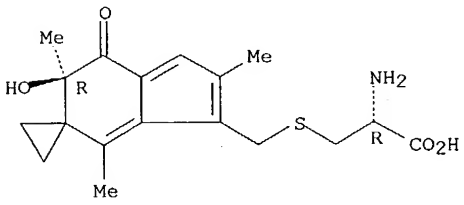
Absolute stereochemistry.



IT **202799-44-8P 238432-50-3P 238432-51-4P**
238432-54-7P 238432-57-0P 238432-58-1P
238432-59-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one derivs. and their amino acid derivs. as antitumor agents)

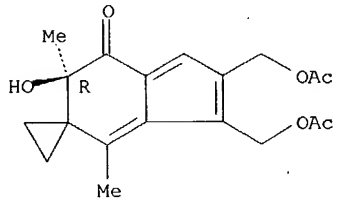
RN 202799-44-8 CAPLUS
CN L-Cysteine, S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



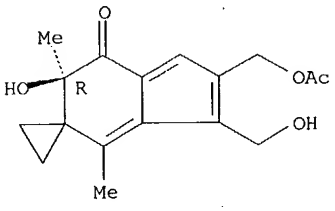
RN 238432-50-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 2',3'-bis[(acetyloxy)methyl]-6'-hydroxy-4',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



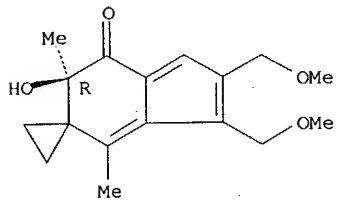
RN 238432-51-4 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 2'-[(acetyloxy)methyl]-6'-hydroxy-3'-(hydroxymethyl)-4',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



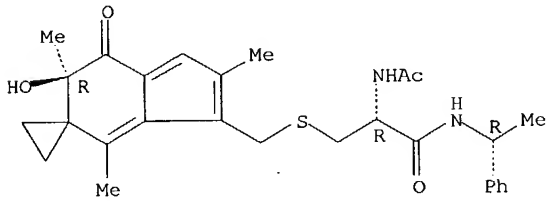
RN 238432-54-7 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',3'-bis(methoxymethyl)-4',6'-dimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



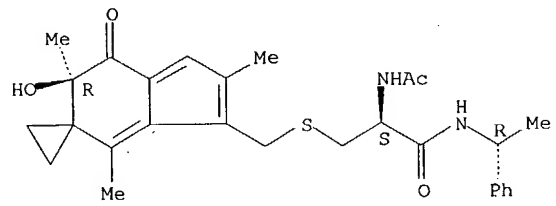
RN 238432-57-0 CAPLUS
CN Propanamide, 2-(acetylamino)-3-[[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]thio]-N-[(1R)-1-phenylethyl]-, (2R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



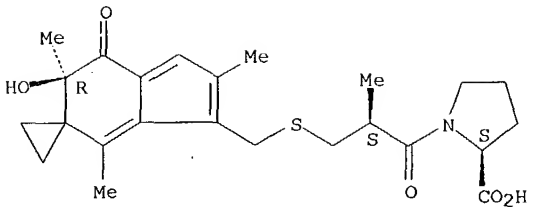
RN 238432-58-1 CAPLUS
CN Propanamide, 2-(acetylamino)-3-[[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]thio]-N-[(1R)-1-phenylethyl]-, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



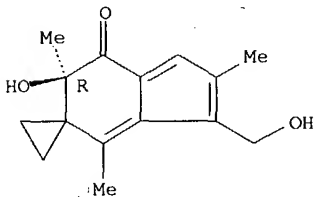
RN 238432-59-2 CAPLUS
CN L-Proline, 1-[(2S)-3-[[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]thio]-2-methyl-1-oxopropyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **158440-71-2**, Hmaf
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one derivs. and their amino acid derivs. as antitumor agents)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 50 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:488227 CAPLUS
DOCUMENT NUMBER: 131:139127
TITLE: Characterization of MGI 114 (HMAF) histiospecific toxicity in human tumor cell lines
AUTHOR(S): Kelner, Michael J.; McMorris, Trevor C.; Montoya, Mark A.; Estes, Leita; Uglik, Sheldon F.; Rutherford, Mary; Samson, Kyra M.; Bagnell, Richard D.; Taetle, Raymond
CORPORATE SOURCE: Dep. Pathology, Med. Center, UCSD, San Diego, CA, 92103, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1999), 44(3), 235-240
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The acylfulvenes are a class of antitumor agents derived from the fungal toxin illudin S. One acylfulvene derivative, MGI 114 (HMAF), demonstrates marked efficacy in xenograft carcinoma models when compared to the parent acylfulvene or related illudin compds. The maximum tolerated dose (MTD) of the 2 analogs in animals, however, is similar. To help elucidate the basis of the increased therapeutic efficacy of MGI 114, the in vitro cytotoxicity, cellular accumulation, and DNA incorporation of this drug was determined and the results were compared with those from the parent acylfulvene analog. The cytotoxicity of acylfulvene analogs was tested in vitro against a variety of tumor cell lines. Radiolabeled MGI 114 was used for cellular accumulation and DNA incorporation studies. MGI 114 retained relative histiospecific toxicity towards myeloid leukemia and various carcinoma cell lines previously noted with the parent acylfulvene compound Markedly fewer intra-cellular mols. of MGI 114 were required to kill human tumor cells in vitro as compared to the parent acylfulvene, indicating that MGI 114 was markedly more toxic on a cellular level. At equitoxic concns., however, the incorporation of MGI 114 into genomic tumor cell DNA was equivalent to that of acylfulvene. Anal. of cellular accumulation of MGI 114 into tumor cells revealed a lower Vmax for tumor cells, and a markedly lower Vd for diffusion accumulation as compared to acylfulvene. The addition of a single methylhydroxyl group to acylfulvene to produce MGI 114 results in a marked increase in cytotoxicity in vitro towards tumor cells as demonstrated by the reduction in IC50 values. There was a corresponding decrease in the number of intracellular mols. of MGI 114 required to kill tumor cells, but no quant. alteration in covalent binding

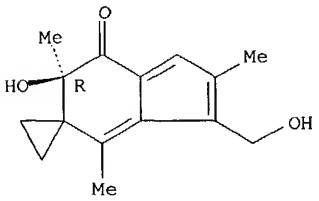
of the drugs to DNA at equitoxic concns. This indicates that cellular metabolism plays a role in the in vitro cytotoxicity of MGI 114. The equivalent incorporation into genomic DNA at equitoxic doses suggests that DNA damage produced by acylfulvene and MGI 114 is equivalent in regard to cellular toxicity and ability to repair DNA. This increased cellular toxicity, together with the decrease in diffusion rate, may explain the increased therapeutic efficacy of MGI 114 as compared to the parent acylfulvene analog.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(histiospecific toxicity of MGI 114 (HMAF) in tumor cell lines compared with acylfulvene analogs)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 51 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1999:399999 CAPLUS

DOCUMENT NUMBER: 131:193895

TITLE: Drug uptake and cellular targets of hydroxymethylacylfulvene (HMAF)

AUTHOR(S): Herzig, Maryanne C. S.; Arnett, Brenda; MacDonald, John R.; Woynarowski, Jan M.

CORPORATE SOURCE: Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, TX, 78245, USA

SOURCE: Biochemical Pharmacology (1999), 58(2), 217-225
CODEN: BCPCA6; ISSN: 0006-2952

PUBLISHER: Elsevier Science Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

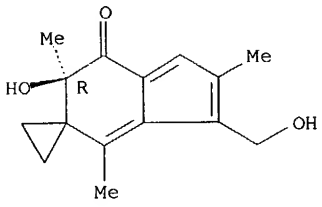
AB Hydroxymethylacylfulvene (HMAF, MGI 114) is a novel antitumor drug and a potent pro-apoptotic agent that has the potential to alkylate cellular nucleophiles. The objective of these studies was to characterize drug uptake and cellular targets for drug binding in human leukemia CEM cells. The uptake of [14C]HMAF had 2 components: a rapid phase (0-10 min) and a slow phase. At 10 μM drug (37°), the rapid and slower phase amounted to 0.86 and 0.13 pmol/min/106 cells, resp. HMAF uptake was inhibited 82% by low temperature (4°) at 4 h. Cell-associated HMAF localized to nuclear (50%), cytoplasmic (37%), and membrane fractions (10%). Continued drug uptake appeared to be driven by covalent binding to cellular macromols. Approx. 1/4 and 2/3 of cell-associated HMAF formed covalent adducts after 10 min and 4 h, resp., as found by perchloric acid precipitation Drug adducts were not readily reversible; 77% of the covalently bound radiolabel was retained by the cells 20 h after drug treatment. Combinations of DNase, RNase, and proteinase K with perchloric acid precipitation showed that .apprx.60, 30, and 10% of the covalently bound drug was associated with the protein, DNA, and RNA fractions, resp. Incubation of 100 μM [14C]HMAF (24 h) with purified DNA, serum albumin, thioredoxin, and thioredoxin reductase resulted in 6, 22, 14, and 11 pmol [14C]HMAF/μg DNA or protein, resp. Apparently, multiple targets for HMAF binding may contribute to the pro-apoptotic and antiproliferative action of the drug.

IT **158440-71-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(drug uptake and cellular targets of hydroxymethylacylfulvene)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



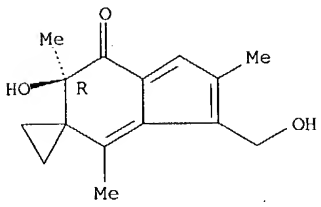
REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 52 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:396074 CAPLUS
DOCUMENT NUMBER: 131:208755
TITLE: Cytotoxic effects of MGI 114 are independent of tumor p53 or p21 expression
AUTHOR(S): Izbicka, Elzbieta; Davidson, Karen; Lawrence, Richard; Cote, Richard; Macdonald, John R.; Von Hoff, Daniel D.
CORPORATE SOURCE: Institute for Drug Development, CTRC Research Foundation, San Antonio, TX, 78245, USA
SOURCE: Anticancer Research (1999), 19(2A), 1299-1307
CODEN: ANTRD4; ISSN: 0250-7005
PUBLISHER: International Institute of Anticancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MGI 114, an analog of illudin S, shows potent activity against a broad range of human tumors in vitro and in vivo, including drug resistant tumors. In this study we examined cytotoxicity of MGI 114 against human tumor cell lines (MCF7, MDA.MB.468, EJ1, J82, SCaBER, KG-1, HL60, and IMR-90) with differing expression of p53 and/or p21 (WAF1) tumor suppressor genes. Only MCF7 and IMR-90 express the wild type p53, WAF1 is present in high levels in MCF7 and SCaBER. WAF1 expression can be induced in KG-1, HL60, and IMR-90. The cells were treated with MGI 114 at 0.1, 1.0 and 10 μg/mL in 1 h exposure and with 0.01, 0.1 and 1.0 μg/mL MGI 114 in a continuous exposure. Cell nos. were measured at days 2, 4, and 7. MGI 114 suppressed growth in all cell lines at day 2 after 1 h exposure at the two highest concns. and at all concns. in a continuous exposure. Some cells partly recovered from the inhibition by day 4. Expression of WAF1 had no apparent effect on growth suppression by MGI 114, however, cells with inducible WAF1 showed slower recovery from MGI 114 inhibition in comparison with the cells under non-permissive conditions. Overall, MGI 114 effectively inhibited growth of human cancer cells regardless of their p53 and WAF1 status.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MGI 114 cytotoxic effects are independent of tumor p53 or p21 expression)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 53 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

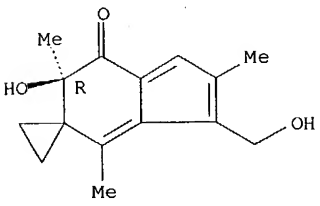
ACCESSION NUMBER: 1999:383512 CAPLUS
DOCUMENT NUMBER: 131:179145
TITLE: Discovery and development of sesquiterpenoid-derived hydroxymethylacylfulvene: a new anticancer drug
AUTHOR(S): McMorris, Trevor C.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, La Jolla, CA, 92093, USA
SOURCE: Bioorganic & Medicinal Chemistry (1999), 7(5), 881-886
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 44 refs. Hydroxymethylacylfulvene (HMAF, MGI 114) is derived from the sesquiterpene illudin S by treatment with dilute H2SO4 and excess paraformaldehyde. It is less cytotoxic than illudin S but exhibits much greater selectivity in toxicity to malignant cells compared to normal cells. HMAF is believed to undergo bioreductive activation in vivo. It is now being tested in human clin. phase II trials against solid tumors.

IT **158440-71-2P**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(discovery and development of sesquiterpenoid-derived hydroxymethylacylfulvene as anticancer drug)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



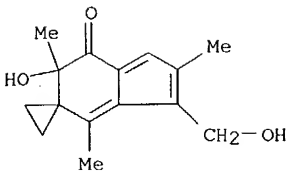
REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 54 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:298756 CAPLUS
DOCUMENT NUMBER: 131:116021
TITLE: A Short Synthesis of the Potent Antitumor Agent (±)-Hydroxymethylacylfulvene Using an Allenic Pauson-Khand Type Cycloaddition
AUTHOR(S): Brummond, Kay M.; Lu, Jianliang
CORPORATE SOURCE: Department of Chemistry, West Virginia University, Morgantown, WV, 26506-6045, USA
SOURCE: Journal of the American Chemical Society (1999), 121(21), 5087-5088
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 131:116021

AB A short synthesis of cis-6',7'-dihydro-2',4',6'-trimethylspiro[cyclopropane-1,5'-[5H]indene]-6',7'-diol and trans-6',7'-dihydro-2',4',6'-trimethylspiro[cyclopropane-1,5'-[5H]indene]-6',7'-diol, intermediates for (±)-hydroxymethylacylfulvene, was reported.

IT **187277-46-9P**, (±)-Hydroxymethylacylfulvene
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of antitumor agent (±)-hydroxymethylacylfulvene via allenic Pauson-Khand cycloaddn.)

RN 187277-46-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

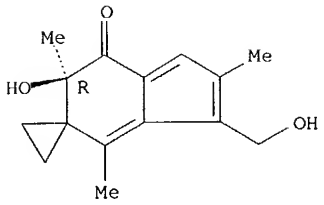
L5 ANSWER 55 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:173597 CAPLUS
DOCUMENT NUMBER: 131:13479
TITLE: Enhanced antitumor activity of 6-hydroxymethylacylfulvene in combination with irinotecan and 5-fluorouracil in the HT29 human colon tumor xenograft model
AUTHOR(S): Britten, Carolyn D.; Hilsenbeck, Susan G.; Eckhardt, S. Gail; Marty, Jennifer; Mangold, Gina; MacDonald, John R.; Rowinsky, Eric K.; Von Hoff, Daniel D.; Weitman, Steve
CORPORATE SOURCE: Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, TX, 78245-3217, USA
SOURCE: Cancer Research (1999), 59(5), 1049-1053
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: AACR Subscription Office
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 6-Hydroxymethylacylfulvene (MGI-114) is a semisynthetic analog of the toxin illudin S, a product of the Omphalotus mushroom. MGI-114 induces cytotoxicity in a variety of solid tumors in vivo, including the refractory HT29 human colon cancer xenograft. The potential application of MGI-114 in the treatment of colon cancer was further explored by evaluating the activity of MGI-114 in combination with irinotecan (CPT-11) and 5-fluorouracil (5FU). Groups of 9 nude mice bearing HT29 xenografts were treated with either single agent MGI-114 CPT-11, or 5FU, or MGI-114 in combination with CPT-11 or 5FU. MGI-114 was administered at 3.5 and 7 mg/kg i.p. daily on days 1 through 5, and CPT-11 and 5FU were administered at 50 and 100 mg/kg i.p. on days 1, 12, and 19. In the single agent studies, MGI-114 CPT-11, and 5FU all resulted in decreased final tumor wts. compared with vehicle-treated controls, but only MGI-114 at 7 mg/kg produced partial responses. When MGI-114 at 3.5 mg/kg was combined with CPT-11, significant decrements in final tumor wts. occurred compared with monotherapy with the same doses of MGI-114 and CPT-11. Also, administration of the low-dose combination (MGI-114 at 3.5 mg/kg and CPT-11 at 50 mg/kg) resulted in final tumor wts. similar to those achieved after administration of high-dose MGI-114 as a single agent. Moreover, the combination of MGI-114 and CPT-11 produced partial responses in nearly all of the animals, with some animals achieving complete responses. The outcome with the combination of MGI-114 and 5FU was less striking, with fewer partial responses and no complete responses. These results suggest enhanced activity when MGI-114 is combined with CPT-11, and clin. trials to further evaluate this combination regimen are planned.

IT **158440-71-2**, MGI-114
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(enhanced antitumor activity of 6-hydroxymethylacylfulvene in combination with irinotecan and 5-fluorouracil in HT29 human colon tumor xenograft model)

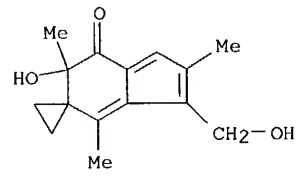
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 56 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:458955 CAPLUS
DOCUMENT NUMBER: 129:95619
TITLE: Part I. Total synthesis of (±)-acylfulvene and (±)-hydroxymethylacylfulvene. Part II. A new synthesis of 2-hydroxyphytanic acid
AUTHOR(S): Hu, Yi
CORPORATE SOURCE: Univ. of California, San Diego, CA, USA
SOURCE: (1998) 228 pp. Avail.: UMI, Order No. DA9820862 From: Diss. Abstr. Int., B 1998, 59(1), 228
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT **187277-46-9P**, (±)-Hydroxymethylacylfulvene
RL: SPN (Synthetic preparation); PREP (Preparation)
(total synthesis of (±)-acylfulvene and (±)-hydroxymethylacylfulvene and a new synthesis of 2-hydroxyphytanic acid)
RN 187277-46-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl- (9CI) (CA INDEX NAME)

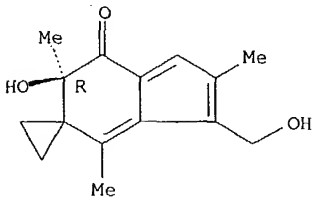


L5 ANSWER 57 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:400146 CAPLUS
DOCUMENT NUMBER: 129:170166
TITLE: Efficacy of MGI 114 (6-hydroxymethylacylfulvene, HMAF) against the mdr1/gp170 metastatic MV522 lung carcinoma xenograft
AUTHOR(S): Kelner, M. J.; Mcmorris, T. C.; Estes, L.; Samson, K. M.; Bagnell, R. D.; Taetle, R.
CORPORATE SOURCE: Department of Pathology, University of California San Diego Medical Center, San Diego, CA, 92103, USA
SOURCE: European Journal of Cancer (1998), 34(6), 908-913 CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Illudins are a novel class of agents with a chemical structure entirely different from current chemotherapeutic agents. A new semisynthetic derivative, HMAF, is markedly effective in a variety of lung, breast and colon carcinoma xenograft models. This analog, MGI 114, is currently in phase I human clin. trials, and is scheduled for 2 different phase II trials. To determine if MGI 114 could be effective in vivo against mdr tumor cells, we generated an mdr1/gp170-pos. clone of the metastatic MV522 human lung carcinoma line by transfecting a eukaryotic expression vector containing the cDNA encoding for the human gp170 protein. This MV522/mdr1 daughter line retained the metastatic ability of parental cells. The parental MV522 xenograft is mildly responsive in vivo to mitomycin C and paclitaxel, as evidenced by partial tumor growth inhibition and a small increase in life span, whereas MV522/mdr1 xenografts were resistant to these agents. In contrast to mitomycin C and paclitaxel, MGI 114 produced xenograft tumor

regressions in 32 of 32 animals and completely eliminated tumors in more than 30% of MV522/mdr1 tumor-bearing mice. Thus, MGI 114 should be effective in vivo against mdr1/gp170-pos. tumors.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MGI 114 activity against mdr1/gp170 metastatic MV522 lung carcinoma xenograft)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



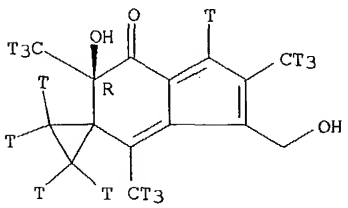
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 58 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:244110 CAPLUS
DOCUMENT NUMBER: 128:321762
TITLE: Synthesis of [3H]-illudin S, [3H]-acylfulvene, [3H]&[14C]-hydroxymethylacylfulvene (MGI 114)
AUTHOR(S): McMorris, Trevor C.; Yu, Jian; Herman, David M.; Kelner, Michael J.; Dawe, Robin; Minamida, Akira
CORPORATE SOURCE: Department Chemistry Biochemistry, University California San Diego, La Jolla, CA, 92093, USA
SOURCE: Journal of Labelled Compounds & Radiopharmaceuticals (1998), 41(4), 279-285
CODEN: JLCRD4; ISSN: 0362-4803
PUBLISHER: John Wiley & Sons Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Tritiated derivs. of the toxic sesquiterpene illudin S have been prepared by fermentation of Omphalotus illudens in the presence of [3H]-sodium acetate. [3H]-illudin S was converted to antitumor [3H]-acylfulvene by treatment with dilute sulfuric acid. Antitumor [14C]-hydroxymethylacylfulvene was best prepared by reacting acylfulvene with [14C]-paraformaldehyde in dilute sulfuric acid.

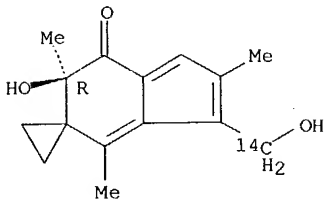
IT **207125-44-8P 207125-45-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of [3H]-illudin S, [3H]-acylfulvene, [3H]&[14C]-hydroxymethylacylfulvene (MGI 114))
RN 207125-44-8 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one-1',2,2,3,3-t5, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-tri(methyl-t3)-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 207125-45-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl-14C)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 59 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:87694 CAPLUS
DOCUMENT NUMBER: 128:167579
TITLE: Preparation of illudin analogs for use as antitumor agents
INVENTOR(S): McMorris, Trevor C.; Kelner, Michael J.
PATENT ASSIGNEE(S): Regents of the University of California, USA; McMorris, Trevor C.; Kelner, Michael J.
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9803458	A1	19980129	WO 1997-US12143	19970714
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5932553	A	19990803	US 1996-683687	19960718
CA 2260926	AA	19980129	CA 1997-2260926	19970714
AU 9736004	A1	19980210	AU 1997-36004	19970714
AU 738991	B2	20011004		
EP 915819	A1	19990519	EP 1997-932586	19970714
EP 915819	B1	20040526		
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CN 1230166	A	19990929	CN 1997-197809	19970714
BR 9710486	A	20000111	BR 1997-10486	19970714
NZ 333857	A	20000929	NZ 1997-333857	19970714
JP 2000515524	T2	20001121	JP 1998-507009	19970714
AT 267791	E	20040615	AT 1997-932586	19970714
EP 1454893	A1	20040908	EP 2004-12220	19970714
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
ZA 9706242	A	19980318	ZA 1997-6242	19970715
NO 9900164	A	19990317	NO 1999-164	19990114
US 6069283	A	20000530	US 1999-241172	19990201
US 6380403	B1	20020430	US 2000-501151	20000209
US 2002161206	A1	20021031	US 2002-134260	20020429
US 6639105	B2	20031028		
US 2004167100	A1	20040826	US 2003-694533	20031027

PRIORITY APPLN. INFO.:		
US 1996-683687	A	19960718
EP 1997-932586	A3	19970714
WO 1997-US12143	W	19970714
US 1999-241172	A1	19990202
US 2000-501151	A1	20000209
US 2002-134260	A3	20020429

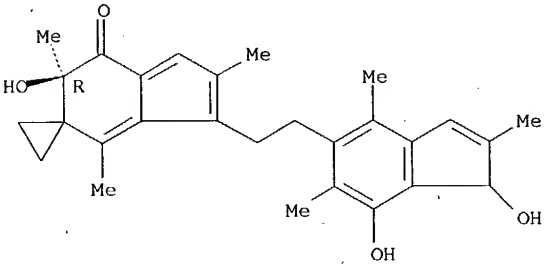
AB Illudin analogs I [R1 = (CH2)nXY; n = 0 - 4; X = O, S, N; Y = groups such as alkylcarboxy, alkylhydroxy, alkylhalo, monosaccharide; R3 = H, alkyl; R4 = H, thioalkyl, thioalkylcarboxylate; R5 = H, OH; R4R5 = bond; R6 = H, alkyl; R7 = OH, silyloxy; R8 = alkyl] were prepared for use as tumor, lymphoma, and leukemia inhibiting agents. Thus, diol II was prepared via

reaction of acylfulvene with acrolein and reduction of the resulting aldehyde with sodium cyanoborohydride. A number of prepared compds. including II were tested for cytotoxic effects against MV522 human lung carcinoma cells and 8392 B-cell leukemia/lymphoma cells.

IT **202799-64-2P 202799-77-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BYP (Byproduct); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of illudin analogs for use as antitumor agents)

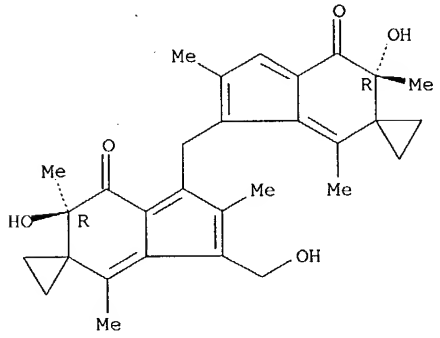
RN 202799-64-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[2-(1,7-dihydroxy-2,4,6-trimethyl-1H-inden-5-yl)ethyl]-6'-hydroxy-2',4',6'-trimethyl-, [5(R)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 202799-77-7 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 1'-[(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)methyl]-6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

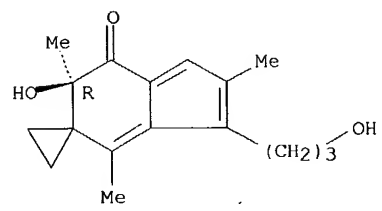
Absolute stereochemistry.



IT **202799-09-5P 202799-11-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of illudin analogs for use as antitumor agents)

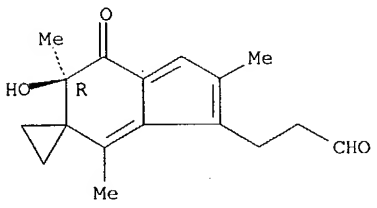
RN 202799-09-5 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(3-hydroxypropyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 202799-11-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]indene]-3'-propanal, 6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxo-, (6'R)- (9CI) (CA INDEX NAME)

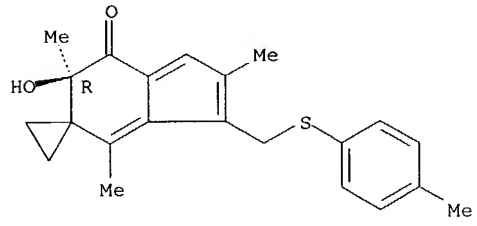
Absolute stereochemistry.



IT **180797-69-7P 197717-56-9P 197717-62-7P**
197717-63-8P 197717-64-9P 197717-75-2P
197717-76-3P 197717-78-5P 197717-79-6P
202799-13-1P 202799-18-6P 202799-20-0P
202799-22-2P 202799-24-4P 202799-26-6P
202799-28-8P 202799-34-6P 202799-42-6P
202799-44-8P 202799-46-0P 202799-48-2P
202799-50-6P 202799-52-8P 202799-54-0P
202799-56-2P 202799-58-4P 202799-62-0P
202799-72-2P 202799-75-5P 202817-54-7P
202817-55-8P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of illudin analogs for use as antitumor agents)

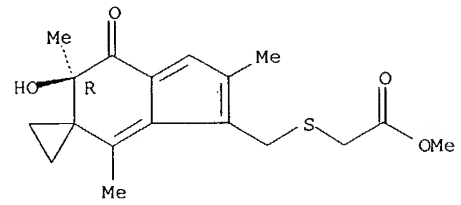
RN 180797-69-7 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',4',6'-trimethyl-3'-[[(4-methylphenyl)thio]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



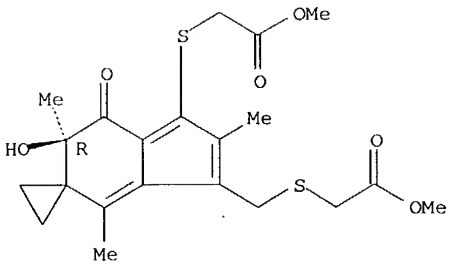
RN 197717-56-9 CAPLUS
CN Acetic acid, [[(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)methyl]thio]-, methyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



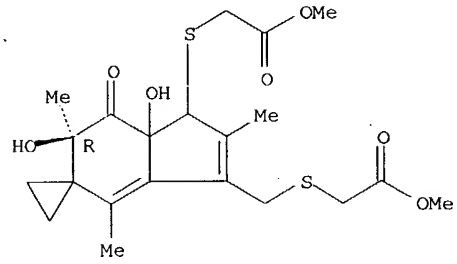
RN 197717-62-7 CAPLUS
CN Acetic acid, [[6',7'-dihydro-6'-hydroxy-3'-[[(2-methoxy-2-oxoethyl)thio]methyl]-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-1'-yl]thio]-, methyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



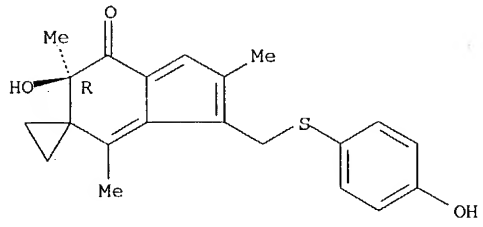
RN 197717-63-8 CAPLUS
CN Acetic acid, [[1',6',7',7'a-tetrahydro-6',7'a-dihydroxy-3'-[[(2-methoxy-2-oxoethyl)thio]methyl]-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-1'-yl]thio]-, methyl ester, (6'R)-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



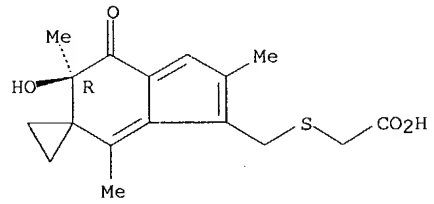
RN 197717-64-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[[(4-hydroxyphenyl)thio]methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



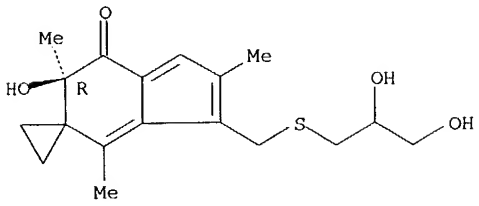
RN 197717-75-2 CAPLUS
CN Acetic acid, [[(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)methyl]thio]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



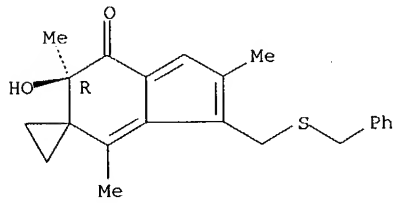
RN 197717-76-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[[(2,3-dihydroxypropyl)thio]methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 197717-78-5 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',4',6'-trimethyl-3'-[[(phenylmethyl)thio]methyl]-, (R)- (9CI) (CA INDEX NAME)

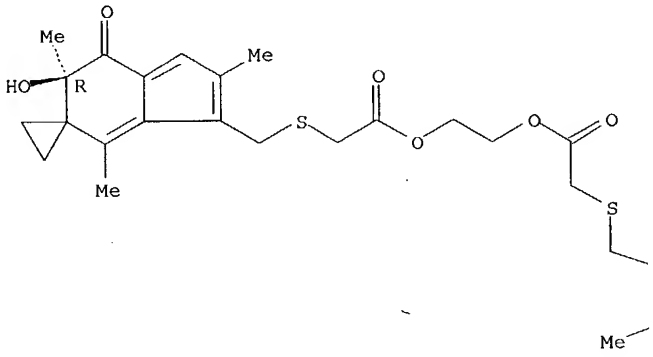
Absolute stereochemistry.

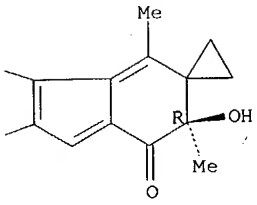


RN 197717-79-6 CAPLUS
CN Acetic acid, [[(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)methyl]thio]-, 1,2-ethanediyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

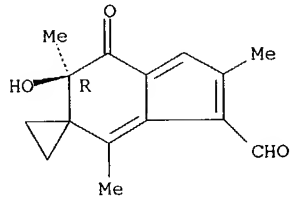
PAGE 1-A





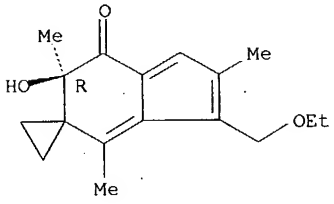
RN 202799-13-1 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]indene]-3'-carboxaldehyde, 6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxo-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



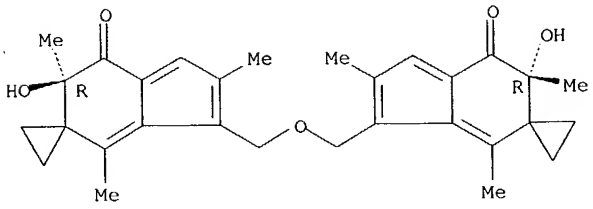
RN 202799-18-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-(ethoxymethyl)-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 202799-20-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-[oxybis(methylene)]bis[6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

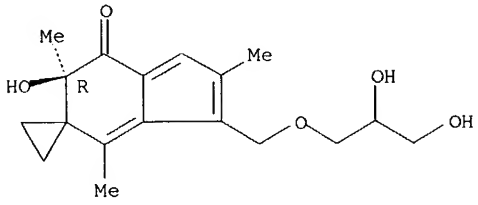
Absolute stereochemistry.



RN 202799-22-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(2,3-

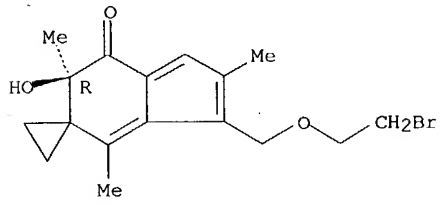
dihydroxypropoxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



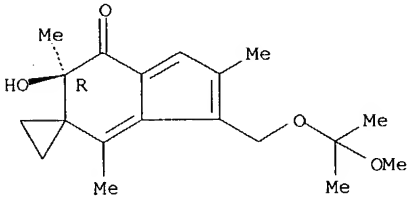
RN 202799-24-4 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(2-bromoethoxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



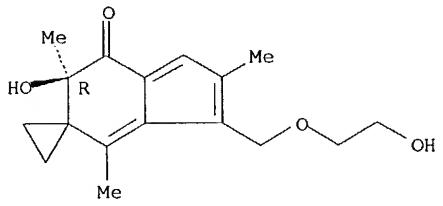
RN 202799-26-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(1-methoxy-1-methylethoxy)methyl]-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



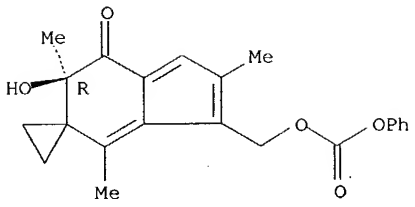
RN 202799-28-8 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(2-hydroxyethoxy)methyl]-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



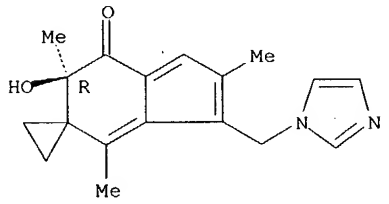
RN 202799-34-6 CAPLUS
CN Carbonic acid, [(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl phenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



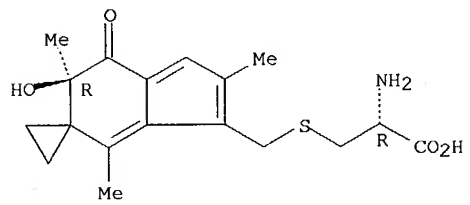
RN 202799-42-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(1H-imidazol-1-ylmethyl)-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



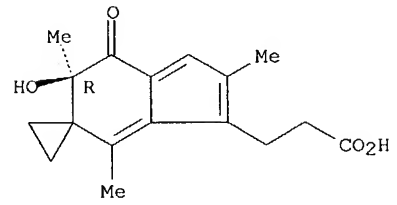
RN 202799-44-8 CAPLUS
CN L-Cysteine, S-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



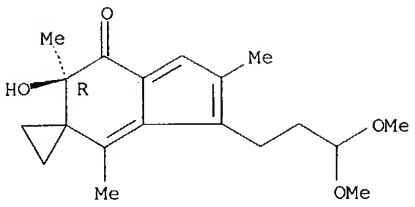
RN 202799-46-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]indene]-3'-propanoic acid, 6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxo-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



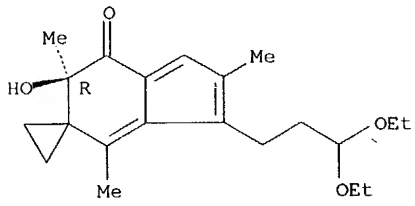
RN 202799-48-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-(3,3-dimethoxypropyl)-6'-hydroxy-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



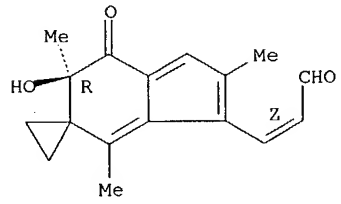
RN 202799-50-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-(3,3-diethoxypropyl)-6'-hydroxy-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



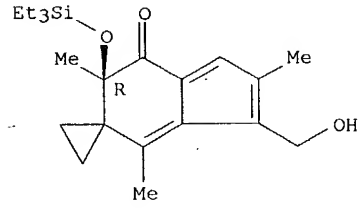
RN 202799-52-8 CAPLUS
CN 2-Propenal, 3-(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)-, [R-(Z)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



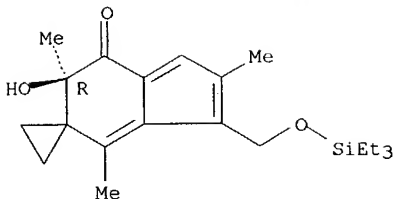
RN 202799-54-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-(hydroxymethyl)-2',4',6'-trimethyl-6'-[(triethylsilyl)oxy]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



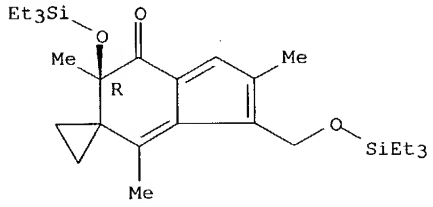
RN 202799-56-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',4',6'-trimethyl-3'-[[(triethylsilyl)oxy]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



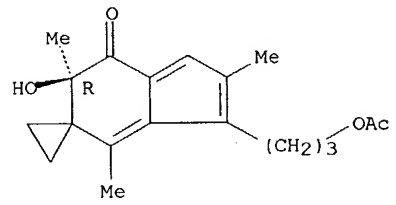
RN 202799-58-4 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 2',4',6'-trimethyl-6'-[(triethylsilyl)oxy]-3'-[[(triethylsilyl)oxy]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



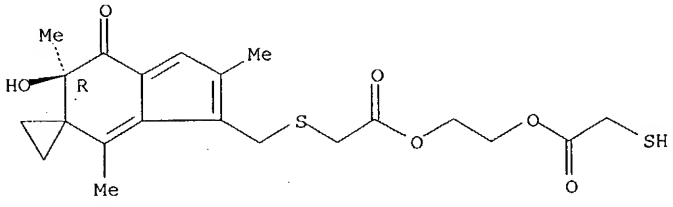
RN 202799-62-0 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[3-(acetyloxy)propyl]-6'-hydroxy-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



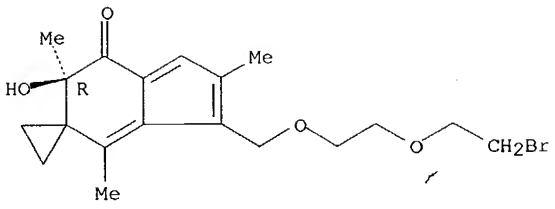
RN 202799-72-2 CAPLUS
CN Acetic acid, [[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]thio]-, 2-[(mercaptoacetyl)oxy]ethyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry.



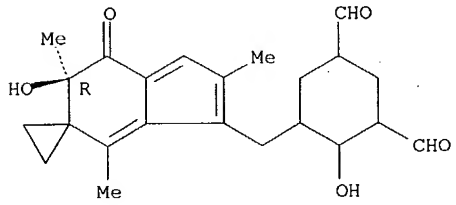
RN 202799-75-5 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[[2-(2-bromoethoxy)ethoxy]methyl]-6'-hydroxy-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 202817-54-7 CAPLUS
CN 1,3-Cyclohexanedicarboxaldehyde, 5-[(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)methyl]-4-hydroxy-, [5(R)]-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

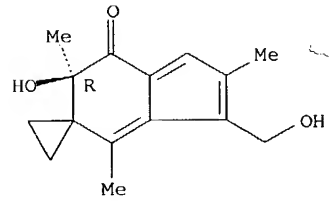


RN 202817-55-8 CAPLUS
CN D-Fructose, O-[[(6'R)-6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl]methyl]- (9CI) (CA INDEX NAME)

CM 1

CRN 158440-71-2
CMF C15 H18 O3

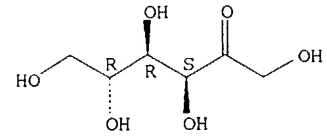
Absolute stereochemistry.



CM 2

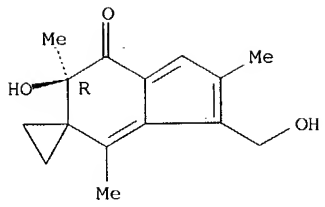
CRN 57-48-7
CMF C6 H12 O6

Absolute stereochemistry.



IT **158440-71-2**, HMAF
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of illudin analogs for use as antitumor agents)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

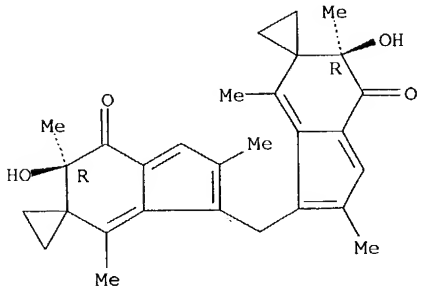
L5 ANSWER 60 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:56100 CAPLUS
DOCUMENT NUMBER: 128:162657
TITLE: Characterization of acylfulvene histiospecific toxicity in human tumor cell lines
AUTHOR(S): Kelner, Michael J.; McMorris, Trevor C.; Montoya, Mark A.; Estes, Leita; Uglik, Slavomir F.; Ruhterford, Mary; Samson, Kyra M.; Bagnell, Richard D.; Taetle, Raymond
CORPORATE SOURCE: Department Pathology 8320, UCSD Medical Center, San Diego, CA, 92103, USA
SOURCE: Cancer Chemotherapy and Pharmacology (1998), 41(3), 237-242
CODEN: CCPHDZ; ISSN: 0344-5704
PUBLISHER: Springer-Verlag
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The therapeutic efficacy of acylfulvene analogs was compared with the parent illudin compds. in terms of their in vitro toxicity, cellular accumulation, and DNA incorporation. The prototype acylfulvene analog retained selective histiospecific toxicity towards myeloid leukemia and various carcinoma cell lines. In vitro killing of tumor cells required ≤30-fold increase in mols. per cell, as compared with illudin S; indicating that acylfulvene is less toxic on a cellular level. At equitoxic concns., acylfulvene incorporation into genomic tumor cell DNA was equivalent to illudin S suggesting that cellular metabolism has a role in acylfulvene cytotoxicity. Anal. of cellular accumulation of acylfulvene into tumor cells revealed a markedly higher Vmax for tumor cells, and a lower Vd for diffusion accumulation into other cells. The authors suggest that the combination of higher Vmax and lower Vd may explain the increased in vivo efficacy of acylfulvene.

IT **137295-69-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cytotoxicity of illudin analogs in cell lines)

RN 137295-69-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-methylenebis[6'-hydroxy-2',4',6'-trimethyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



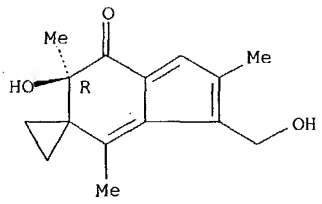
L5 ANSWER 61 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:752596 CAPLUS
DOCUMENT NUMBER: 128:70470

TITLE: Effects on DNA integrity and apoptosis induction by a novel antitumor sesquiterpene drug, 6-hydroxymethylacylfulvene (HMAF, MGI 114)
AUTHOR(S): Woynarowski, Jan M.; Napier, Cheryl; Koester, Steven K.; Chen, Shih-Fong; Troyer, Dean; Chapman, William; Macdonald, John R.
CORPORATE SOURCE: CANCER THERAPY AND RESEARCH CENTER, SAN ANTONIO, TX, 78245-3217, USA
SOURCE: Biochemical Pharmacology (1997), 54(11), 1181-1193
CODEN: BCPCA6; ISSN: 0006-2952
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 6-Hydroxymethylacylfulvene (HMAF, MGI 114) is a new alkylating antitumor sesquiterpenoid with promising and often curative antitumor activity in vivo. This study examined the ability of the drug to damage cellular DNA, induce apoptosis, and affect the cell cycle of CEM human leukemia cells. No bifunctional lesions, interstrand DNA cross-links or DNA-protein cross-links were seen (by alkaline sedimentation and K+/SDS precipitation, resp.) when using ≤50 μM HMAF. The drug possibly formed some monoadducts, as DNA from drug-treated cells impeded primer extension by Taq polymerase, although only partial inhibition was seen even at 200 μM HMAF. HMAF also induced secondary lesions in cellular DNA, single-strand breaks that were detectable (by nucleoid sedimentation and alkaline sucrose gradient anal.) after a 4-h treatment at HMAF levels as low as 2 μM, comparable to the growth inhibition IC50 value (1.7 μM). A post-treatment incubation of cells in drug-free medium generated substantial amts. of DNA double-stranded fragments of several kbp, suggesting apoptotic fragmentation (>30% of total DNA following treatment with 20 μM HMAF and a 17-h post-treatment incubation). Chromatin condensation (by ultrastructural anal.) and induction of sub-G1 particles and apoptotic strand breakage (by multiparametric flow cytometry) confirmed induction of apoptosis by HMAF. HMAF preferentially inhibited DNA synthesis (IC50 ≈ 2 μM), which is consistent with an S phase block, observed by cell cycle anal. The pattern of apoptotic DNA fragmentation, inhibition of DNA synthesis, and blockage in the S phase suggests that these events play a role in the antiproliferative activity of HMAF.

IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effects on DNA integrity and apoptosis induction by novel antitumor sesquiterpene drug hydroxymethylacylfulvene (MGI 114))
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 62 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:714693 CAPLUS
DOCUMENT NUMBER: 127:319104
TITLE: Reaction of antitumor hydroxymethylacylfulvene (HMAF) with thiols
AUTHOR(S): Mcmorris, Trevor C.; Yu, Jian; Estes, Leita A.; Kelner, Michael J.
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California, La Jolla, CA, 92093-0506, USA
SOURCE: Tetrahedron (1997), 53(43), 14579-14590
CODEN: TETRAB; ISSN: 0040-4020
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal

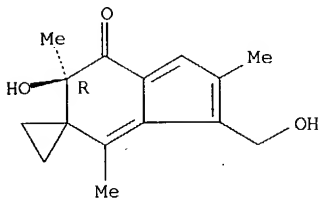
LANGUAGE: English
OTHER SOURCE(S): CASREACT 127:319104

AB Hydroxymethylacylfulvene (HMAF), also designated MGI-114, a semisynthetic derivative of the toxic sesquiterpene illudin S, has potent antitumor properties and is currently in clin. trials. HMAF was reacted with thiols at neutral and acidic pH to form novel products in which the primary allylic hydroxyl was displaced by thiol. E.g., reaction of HMAF with Me thioglycolate resulted in the formation of sulfides I and II (RR1 = bond; R = OH, R1 = H). When tested for anticancer activity against MV522 metastatic lung carcinoma cells, sulfides II gave IC50 values >3 nM compared to 73 ± 8 for HMAF.

IT **158440-71-2**, HMAF
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(preparation and antitumor activity of sulfides obtained by reacting hydroxymethylacylfulvene (HMAF) with thiols)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

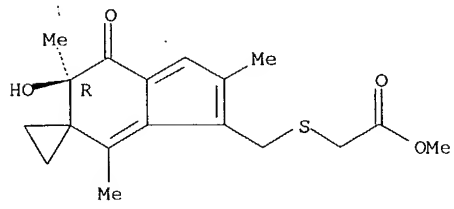
Absolute stereochemistry.



IT **197717-56-9P 197717-62-7P 197717-63-8P**
197717-64-9P 197717-76-3P 197717-78-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of sulfides obtained by reacting hydroxymethylacylfulvene (HMAF) with thiols)

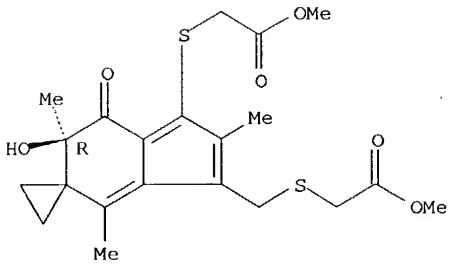
RN 197717-56-9 CAPLUS
CN Acetic acid, [[(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)methyl]thio]-, methyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



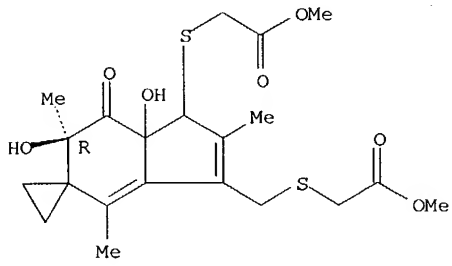
RN 197717-62-7 CAPLUS
CN Acetic acid, [[6',7'-dihydro-6'-hydroxy-3'-[[(2-methoxy-2-oxoethyl)thio]methyl]-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-1'-yl]thio]-, methyl ester, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



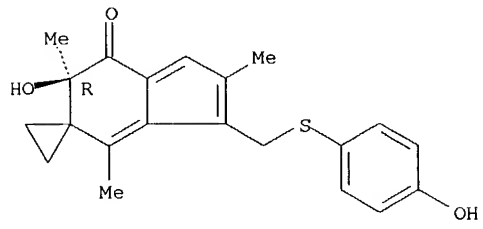
RN 197717-63-8 CAPLUS
CN Acetic acid, [[1',6',7',7'a-tetrahydro-6',7'a-dihydroxy-3'-[[(2-methoxy-2-oxoethyl)thio]methyl]-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-1'-yl]thio]-, methyl ester, (6'R)-[partial]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



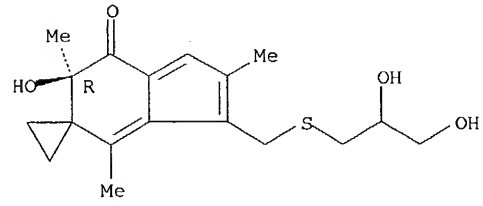
RN 197717-64-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[[(4-hydroxyphenyl)thio]methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



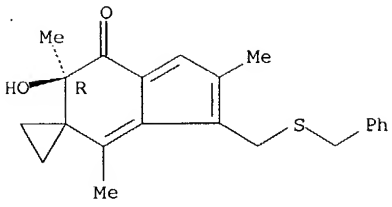
RN 197717-76-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[[(2,3-dihydroxypropyl)thio]methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



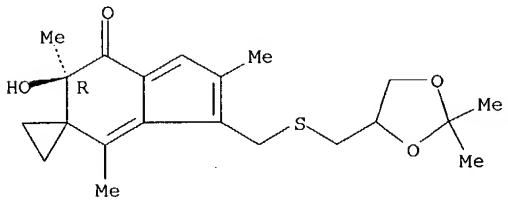
RN 197717-78-5 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',4',6'-trimethyl-3'-[[(phenylmethyl)thio]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



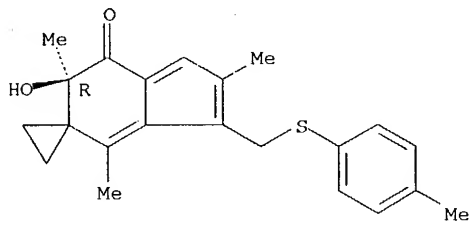
IT **197717-77-4P**
RL: BYP (Byproduct); PREP (Preparation)
(preparation and antitumor activity of sulfides obtained by reacting hydroxymethylacylfulvene (HMAF) with thiols)
RN 197717-77-4 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[[[(2,2-dimethyl-1,3-dioxolan-4-yl)methyl]thio]methyl]-6'-hydroxy-2',4',6'-trimethyl-, [4(R)]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



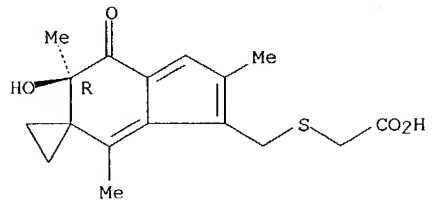
IT **180797-69-7P 197717-75-2P 197717-79-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antitumor activity of sulfides obtained by reacting hydroxymethylacylfulvene (HMAF) with thiols)
RN 180797-69-7 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',4',6'-trimethyl-3'-[[(4-methylphenyl)thio]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 197717-75-2 CAPLUS
CN Acetic acid, [[(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)methyl]thio]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

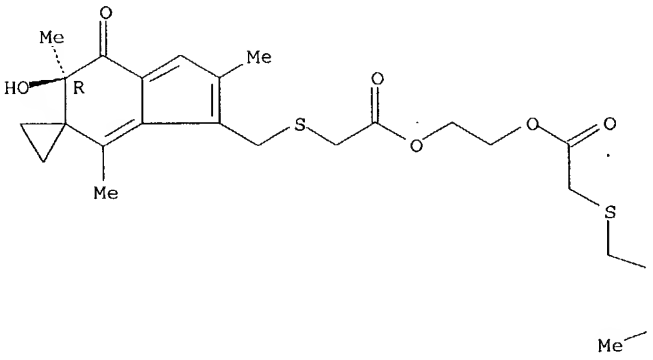


RN 197717-79-6 CAPLUS
CN Acetic acid, [[(6',7'-dihydro-6'-hydroxy-2',4',6'-trimethyl-7'-

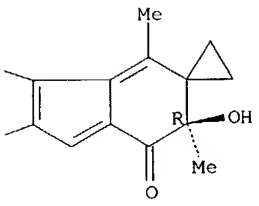
oxospiro[cyclopropane-1,5'-[5H]inden]-3'-yl)methyl]thio}-, 1,2-ethanediyl ester, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



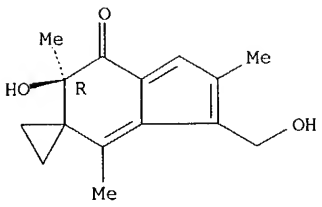
PAGE 1-B



REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

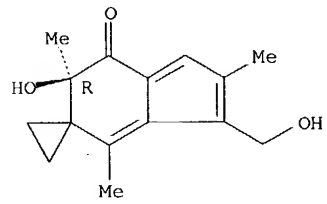
L5 ANSWER 63 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:516889 CAPLUS
DOCUMENT NUMBER: 127:220809
TITLE: Synthesis of acylfulvenes and analogs of the antitumor agent hydroxymethylacylfulvene (HMAF) (illudin s)
AUTHOR(S): Yu, Jian
CORPORATE SOURCE: Univ. of California, San Diego, CA, USA
SOURCE: (1997) 157 pp. Avail.: UMI, Order No. DA9726905
From: Diss. Abstr. Int., B 1997, 58(3), 1297
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT **158440-71-2P**, HMAF
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of acylfulvenes and analogs of the antitumor agent hydroxymethylacylfulvene (HMAF))
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 64 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:187282 CAPLUS
DOCUMENT NUMBER: 126:225420
TITLE: An acetal derivative of illudin S with improved antitumor activity
AUTHOR(S): McMorris, Trevor C.; Yu, Jian; Gantzel, Peter K.; Estes, Leita A.; Kelner, Michael J.
CORPORATE SOURCE: Dep. Chemistry Biochemistry, Univ. California, La Jolla, CA, 92093-0506, USA
SOURCE: Tetrahedron Letters (1997), 38(10), 1697-1698
CODEN: TELEAY; ISSN: 0040-4039
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Methylene acetal of an epimer of illudin S was obtained by treating illudin S with a large excess of paraformaldehyde in 1N H2SO4 solution X-ray crystallog. anal. showed that the configuration at the allylic carbon has been inverted. This acetal was found to be less toxic and showed a higher therapeutic index than illudin S.
IT **158440-71-2P**, HMAF
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of an acetal derivative of illudin S with improved antitumor activity)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

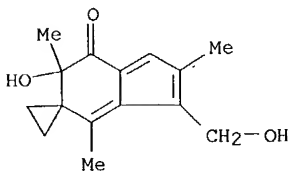
Absolute stereochemistry.



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 65 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:138655 CAPLUS
DOCUMENT NUMBER: 126:171729
TITLE: Total synthesis of hydroxymethylacylfulvene, an antitumor derivative of illudin S
AUTHOR(S): McMorris, Trevor C.; Hu, Yi; Yu, Jian; Kelner, Michael J.
CORPORATE SOURCE: Department Chemistry Biochemistry, University California, San Diego, La Jolla, CA, 92093, USA
SOURCE: Chemical Communications (Cambridge) (1997), (3), 315-316
CODEN: CHCOFS; ISSN: 1359-7345
PUBLISHER: Royal Society of Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 126:171729
AB (±)-Hydroxymethylacylfulvene (I) is synthesized in 14 steps from 4-hydroxy-5-methyl-2-cyclopenten-1-one and 1-acetyl-1-(diazoacetyl)cyclopropane in 15% overall yield.
IT **187277-46-9P**, (±)-Hydroxymethylacylfulvene
RL: SPN (Synthetic preparation); PREP (Preparation)

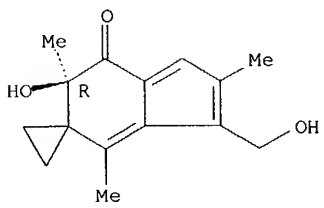
(total synthesis of hydroxymethylacylfulvene)
RN 187277-46-9 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 66 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:71621 CAPLUS
DOCUMENT NUMBER: 126:166163
TITLE: Preclinical antitumor activity of 6-hydroxymethylacylfulvene, a semisynthetic derivative of the mushroom toxin illudin S
AUTHOR(S): MacDonald, John R.; Muscoplat, Charles C.; Dexter, Daniel L.; Mangold, Gina L.; Chen, Shih-Fong; Kelner, Michael J.; McMorris, Trevor C.; Von Hoff, Daniel D.
CORPORATE SOURCE: MGI PHARMA, Inc., Minnetonka, MN, 55343-9667, USA
SOURCE: Cancer Research (1997), 57(2), 279-283
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB 6-Hydroxymethylacylfulvene (HMAF; MGI 114) is a novel semisynthetic antitumor agent derived from the sesquiterpene mushroom toxin illudin S. In vitro cytotoxicity detns. produced IC50 concns. (concns. required for 50% inhibition of growth) ranging from 160 nM in sensitive MCF-7 human mammary carcinoma cells to 17 μM in relatively insensitive murine B16 melanoma cells. In vivo antitumor activity was consistent with in vitro sensitivity. HMAF was very effective in human tumor xenograft models, including MX-1 breast carcinoma, MV522 lung adenocarcinoma, and HT-29 colon carcinoma, but not murine B16 melanoma or P388 leukemia. Excellent responses were observed in animals bearing MX-1 tumors administered i.v. or i.p. doses of 3-7.5 mg/kg daily for 5 days, with complete regression recorded in 29 of 30 animals administered i.v. HMAF. Extensive tumor shrinkage was also observed with MV522, and significant tumor growth inhibition was obtained with HT-29 when animals received 5 daily i.p. doses ranging from 3.75 to 7.5 mg/kg. Complete regressions were also observed in individual animals with MV522 and HT-29. The excellent activity of HMAF in several human solid tumor xenografts, including the more refractory MV522 and HT-29 models, warrants the further investigation of this novel agent in clin. trials.
IT **158440-71-2**, MGI 114
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preclin. antitumor activity of 6-hydroxymethylacylfulvene, a semisynthetic derivative of the mushroom toxin illudin S)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

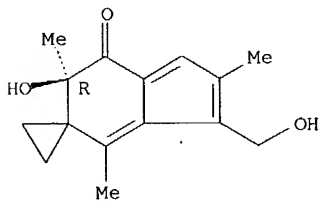
L5 ANSWER 67 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:714632 CAPLUS
DOCUMENT NUMBER: 126:630
TITLE: Efficacy of HMAF (MGI-114) in the MV522 metastatic lung carcinoma xenograft model nonresponsive to traditional anticancer agents
AUTHOR(S): Kelner, Michael J.; McMorris, Trevor C.; Estes, Leita; Wang, Wen; Samson, Kyra M.; Taetle, Raymond
CORPORATE SOURCE: Department Pathology, UCSD, San Diego, 92103, USA
SOURCE: Investigational New Drugs (1996), 14(2), 161-167
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Illudin analogs are cytotoxic to a variety of multidrug resistant cell lines, and display an unusual toxicity towards DNA helicase-deficient cell lines. Earlier illudin analogs demonstrated efficacy in several xenograft models, including a metastatic MV522 lung cancer model, resistant to conventional anticancer agents. These illudin analogs prolonged life span as compared to conventional agents, but did not induce complete remission of primary tumors. In vitro screening studies identified a semisynthetic derivative, hydroxymethylacylfulvene (HMAF, MGI-114), with increased selective cytotoxicity towards carcinoma cells. The HMAF analog was markedly effective in the exptl. MV522 metastasizing lung carcinoma xenograft system, a model refractory to treatment with existing anticancer agents. Treatment with paclitaxel, doxorubicin, or cisplatin failed to significantly inhibit primary tumor growth or prolong life span of MV522 tumor-bearing animals. Treatment with mitomycin C at the LD20 increased life span in surviving animals up to 61%. Treatment with HMAF induced primary tumor regression in all animals and increased life span greater than 150%. Thus, administration of HMAF inhibited development of lung metastasis in a model refractory to treatment with conventional anticancer agents. These results support further evaluation of HMAF as a therapeutic agent for treatment of solid tumors such as adenocarcinoma of the lung.

IT **158440-71-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor effects of hydroxymethylacylfulvene in lung cancer xenograft model nonresponsive to traditional anticancer agents)

RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 68 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:672853 CAPLUS
DOCUMENT NUMBER: 126:1174
TITLE: Illudin analogs useful as antitumor agents, and their preparation
INVENTOR(S): Kelner, Michael J.; McMorris, Trevor C.; Taetle, Raymond
PATENT ASSIGNEE(S): The Regents of the University of California, USA
SOURCE: U.S., 19 pp., Cont.-in-part of U.S. 5,439,936.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5563176	A	19961008	US 1994-276169	19940715
US 5439942	A	19950808	US 1990-606511	19901031
US 5439936	A	19950808	US 1993-15179	19930209
PRIORITY APPLN. INFO.:			US 1989-416395 B2	19891003
			US 1990-606511 A2	19901031
			US 1993-15179 A2	19930209

OTHER SOURCE(S): MARPAT 126:1174

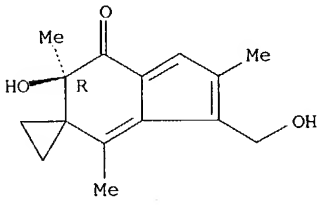
AB Antineoplastic illudin analogs I [R4-R6 = C1-4 alkyl; Y = H, C1-3 alkyl, (R4)(R5)(R6)Si, alkanoyl ((C1-4)alkyl-C(O)); R = CH2OH, halo, (OY-substituted) benzyl, alkanoylmethyl (CH2OC(O)R7); R7 = C1-4 alkyl, C6-12 aryl, NX2; X = H, C1-4 alkyl], and pharmaceutically acceptable salts thereof, are provided. Analog preparation, in vitro and in vivo antitumor activities, and structure-activity relationships are included.

IT **158440-71-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(illudin analog preparation for antitumor agents)

RN 158440-71-2 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

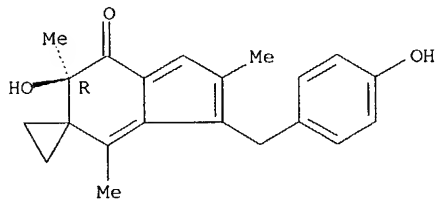


IT **158440-74-5P 158440-75-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(illudin analog preparation for antitumor agents)

RN 158440-74-5 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(4-hydroxyphenyl)methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

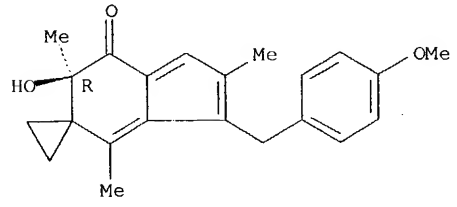
Absolute stereochemistry.



RN 158440-75-6 CAPLUS

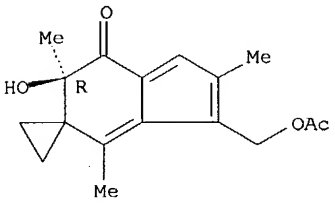
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(4-methoxyphenyl)methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



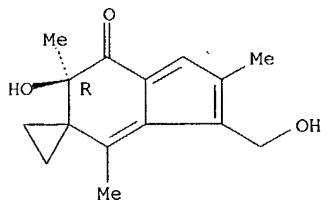
IT **168204-03-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(illudin analog preparation for antitumor agents)
RN 168204-03-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(acetyloxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



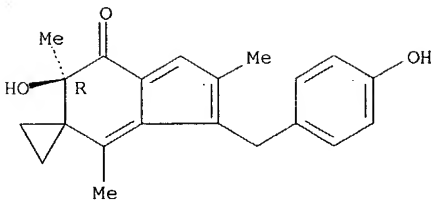
L5 ANSWER 69 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:531662 CAPLUS
DOCUMENT NUMBER: 125:196032
TITLE: (Hydroxymethyl)acylfulvene: An Illudin Derivative with Superior Antitumor Properties
AUTHOR(S): McMorris, Trevor C.; Kelner, Michael J.; Wang, Wen; Yu, Jian; Estes, Leita A.; Taetle, Raymond
CORPORATE SOURCE: Department of Chemistry and Biochemistry, University of California at San Diego, Jolla, CA, 92093-0506, USA
SOURCE: Journal of Natural Products (1996), 59(9), 896-899
CODEN: JNPRDF; ISSN: 0163-3864
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Reaction of the fungal sesquiterpene illudin S with excess paraformaldehyde in dilute H2SO4 gives (hydroxymethyl)acylfulvene (I, R = OH). The primary allylic hydroxyl thus formed can undergo very facile replacement by a variety of nucleophiles, giving I [R = 4-HOC6H4, 4-MeOC6H4, 4-MeC6H4S]. I [R = OH] was more toxic than acylfulvene, but less toxic than illudin S to HL 60 cells.
IT **158440-71-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation and antitumor activity of hydroxymethylacylfulvene)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



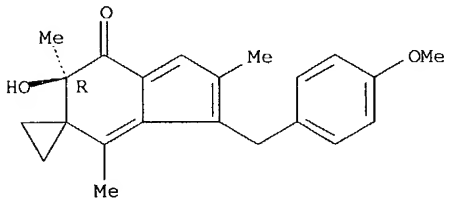
IT **158440-74-5P 158440-75-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of hydroxymethylacylfulvene)
RN 158440-74-5 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(4-hydroxyphenyl)methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



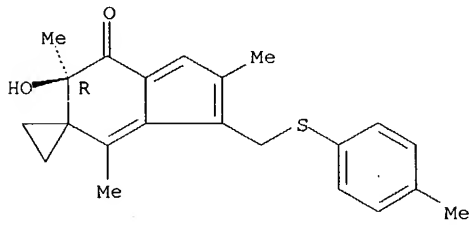
RN 158440-75-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(4-methoxyphenyl)methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



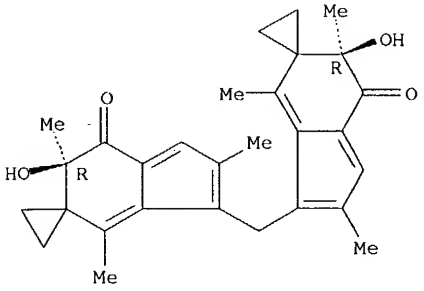
IT **180797-69-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antitumor activity of hydroxymethylacylfulvene)
RN 180797-69-7 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-2',4',6'-trimethyl-3'-[[(4-methylphenyl)thio]methyl]-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 70 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:98922 CAPLUS
DOCUMENT NUMBER: 124:219578
TITLE: Acylfulvenes, a new class of potent antitumor agents
AUTHOR(S): McMorris, T. C.; Kelner, M. J.; Wang, W.; Diaz, M. A.; Estes, L. A.; Taetle, R.
CORPORATE SOURCE: Dep. Chem. Pathol., Univ. California, San Diego, CA, 92093-0506, USA
SOURCE: Experientia (1996), 52(1), 75-80
CODEN: EXPEAM; ISSN: 0014-4754
PUBLISHER: Birkhaeuser
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Acylfulvene, derived from the sesquiterpene illudin S by treatment with acid (reverse Prins reaction), is far less reactive to thiols than illudin S. However, it is reduced readily to an aromatic product, in the same way as illudin S. This may explain its greatly improved therapeutic index compared to that of the parent compound
IT **137295-69-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(acylfulvenes, a new class of potent antitumor agents)
RN 137295-69-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-methylenebis[6'-hydroxy-2',4',6'-trimethyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



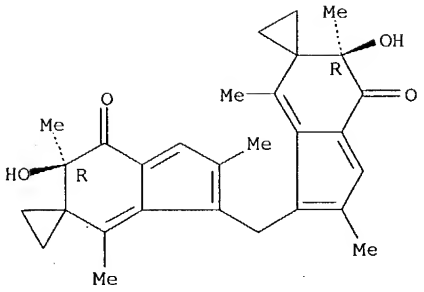
L5 ANSWER 71 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:916203 CAPLUS
DOCUMENT NUMBER: 124:75717
TITLE: Efficacy of acylfulvene illudin analog against a metastatic lung carcinoma MV522 xenograft nonresponsive to traditional anticancer agents: retention of activity against various mdr phenotypes and unusual cytotoxicity against ERCC2 and ERCC3 DNA helicase-deficient cells
AUTHOR(S): Kelner, Michael J.; McMorris, Trevor C.; Estes, Leita; Starr, Robin J.; Rutherford, Mary; Montoya, Mark; Samson, Kyra M.; Taetle, Raymond
CORPORATE SOURCE: Dept. Pathology, UCSD Medical Center, San Diego, CA, 92103-8320, USA
SOURCE: Cancer Research (1995), 55(21), 4936-40
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Four second-generation Illudin analogs were synthesized and tested for antitumor activity using a metastatic lung carcinoma xenograft model resistant to conventional antitumor agents. One analog, the parent illudofulvene-derivative called Acylfulvene, inhibited xenograft primary tumor growth and prolonged life span of tumor-bearing animals when administered i.p. or i.v. The efficacy of Acylfulvene exceeded that of mitomycin C, cisplatin, paclitaxol, the parent compound Illudin S, and an earlier analog, dehydroilludin M. Promising features of this new analog are: (a) the retention in vitro activity against a variety of mdr tumor phenotypes including gp170+, gp150+, GSHTR-Pi, topoisomerase I, and topoisomerase II mutants; and (b) an apparent selective cytotoxicity toward cells deficient in either ERCC2 or ERCC3 DNA helicase activity.

IT **137295-69-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(illudin analog inhibition of metastatic lung carcinoma xenograft nonresponsive to traditional anticancer agents, and activity against various mdr phenotypes and unusual cytotoxicity against ERCC2 and ERCC3 DNA helicase-deficient cells)

RN 137295-69-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-methylenebis[6'-hydroxy-2',4',6'-trimethyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 72 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:806662 CAPLUS
DOCUMENT NUMBER: 123:218398
TITLE: Method of treating certain tumors using illudin analogs
INVENTOR(S): Kelner, Michael J.; McMorris, Trevor C.; Taetle, Raymond
PATENT ASSIGNEE(S): University of California, USA
SOURCE: U.S., 15 pp. Cont.-in-part of U.S. Ser. No. 416,395, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

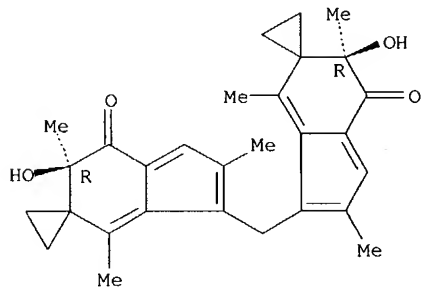
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5439942	A	19950808	US 1990-606511	19901031
CA 2067365	AA	19910404	CA 1990-2067365	19901002
IL 95875	A1	19941021	IL 1990-95875	19901002
AT 141802	E	19960915	AT 1990-916968	19901002
ES 2091249	T3	19961101	ES 1990-916968	19901002
US 5439936	A	19950808	US 1993-15179	19930209
US 5563176	A	19961008	US 1994-276169	19940715
US 5523490	A	19960604	US 1994-332940	19941101
PRIORITY APPLN. INFO.:			US 1989-416395 B2	19891003
			US 1990-606511 A2	19901031
			US 1993-15179 A2	19930209

AB A method of inhibiting certain tumor cell growth in a subject is provided, comprising contacting the tumor with a therapeutic amount of an illudin S or illudin M analog I (R1 = H, R2 = Me, R3 = OH), where the analog is capable of inhibiting tumor cell growth without excessive toxicity to the subject.

IT **137295-69-3**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(illudin analogs and preparation thereof for tumor treatment)

RN 137295-69-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-methylenebis[6'-hydroxy-2',4',6'-trimethyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 73 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1995:806661 CAPLUS

DOCUMENT NUMBER: 123:218397
TITLE: Method of treating certain tumors using illudin analogs
INVENTOR(S): Kelner, Michael J.; McMorris, Trevor C.; Taetle, Raymond
PATENT ASSIGNEE(S): University of California, USA
SOURCE: U.S., 21 pp. Cont.-in-part of U.S. Ser. No. 606,511. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5439936	A	19950808	US 1993-15179	19930209
US 5439942	A	19950808	US 1990-606511	19901031
CA 2155329	AA	19940818	CA 1994-2155329	19940202
WO 9418151	A1	19940818	WO 1994-US1232	19940202
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9461700	A1	19940829	AU 1994-61700	19940202
AU 676889	B2	19970327		
BR 9405689	A	19951121	BR 1994-5689	19940202
EP 683762	A1	19951129	EP 1994-908702	19940202
EP 683762	B1	19981223		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1119854	A	19960403	CN 1994-191560	19940202
CN 1046934	B	19991201		
HU 72450	A2	19960429	HU 1995-2358	19940202
HU 220059	B	20011028		
JP 08506812	T2	19960723	JP 1994-518208	19940202
PL 175024	B1	19981030	PL 1994-310159	19940202
AT 174894	E	19990115	AT 1994-908702	19940202
ES 2125441	T3	19990301	ES 1994-908702	19940202
RU 2145849	C1	20000227	RU 1995-121694	19940202
MD 1418	F2	20000229	MD 1996-960212	19940202
CZ 288596	B6	20010711	CZ 1995-1986	19940202
US 5563176	A	19961008	US 1994-276169	19940715
US 5523490	A	19960604	US 1994-332940	19941101
NO 9503099	A	19951009	NO 1995-3099	19950807

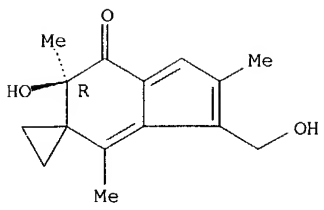
PRIORITY APPLN. INFO.:		
US 1989-416395	B2	19891003
US 1990-606511	A2	19901031
US 1993-15179	A	19930209
WO 1994-US1232	W	19940202

AB A therapeutic method to inhibit tumor cell growth in a subject is provided, comprising parenterally administering a therapeutic amount of I [R = CH2OH, CH2OC(O)Me, p-(CH2PhOH), p-(CH2PhOMe), I, Br] in a pharmaceutically acceptable carrier, where the tumor cell is sensitive to inhibition by I and is selected from the group consisting of a myeloid leukemia cell, a T-cell leukemia cell, a lung carcinoma cell, an ovarian carcinoma cell, and a breast carcinoma cell. Preparation and activity of I are included.

IT **158440-71-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(illudin analogs for tumor treatment and their preparation)

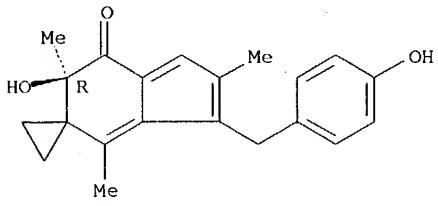
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



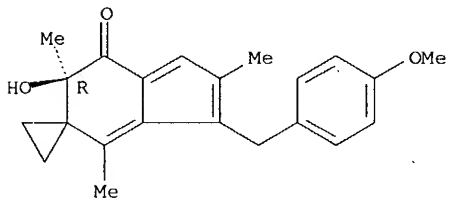
IT **158440-74-5P 158440-75-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(illudin analogs for tumor treatment and their preparation)
RN 158440-74-5 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(4-hydroxyphenyl)methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



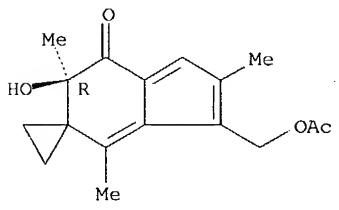
RN 158440-75-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(4-methoxyphenyl)methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **168204-03-3**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(illudin analogs for tumor treatment and their preparation)
RN 168204-03-3 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3'-[(acetyloxy)methyl]-6'-hydroxy-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

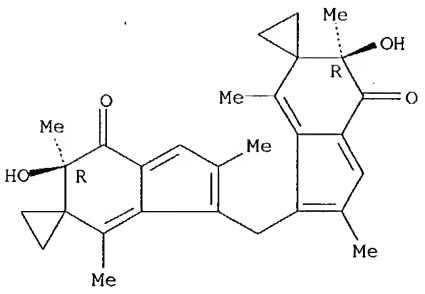
Absolute stereochemistry.



IT **137295-69-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(illudin analogs for tumor treatment and their preparation)
RN 137295-69-3 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-methylenebis[6'-hydroxy-2',4',6'-trimethyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



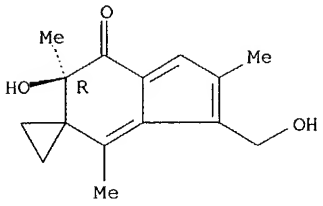
L5 ANSWER 74 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1994:630392 CAPLUS
DOCUMENT NUMBER: 121:230392
TITLE: Acylfulvene-analog antitumor agents
INVENTOR(S): Kelner, Michael J.; McMorris, Trevor C.; Taetle, Raymond
PATENT ASSIGNEE(S): Regents of the University of California, USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9418151	A1	19940818	WO 1994-US1232	19940202
W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5439936	A	19950808	US 1993-15179	19930209
AU 9461700	A1	19940829	AU 1994-61700	19940202
AU 676889	B2	19970327		
BR 9405689	A	19951121	BR 1994-5689	19940202
EP 683762	A1	19951129	EP 1994-908702	19940202
EP 683762	B1	19981223		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08506812	T2	19960723	JP 1994-518208	19940202
PL 175024	B1	19981030	PL 1994-310159	19940202
RU 2145849	C1	20000227	RU 1995-121694	19940202
MD 1418	F2	20000229	MD 1996-960212	19940202
NO 9503099	A	19951009	NO 1995-3099	19950807

PRIORITY APPLN. INFO.:	US 1993-15179	A	19930209
	US 1989-416395	B2	19891003
	US 1990-606511	A2	19901031
	WO 1994-US1232	W	19940202

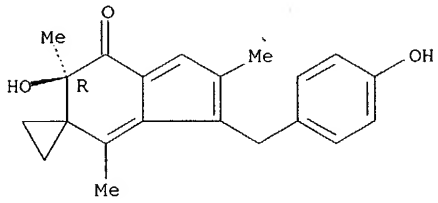
OTHER SOURCE(S): MARPAT 121:230392
AB Inhibiting tumor cell growth in a subject comprises treating the tumor with a therapeutic amount of the title compds. [I; R = CH2OH, CH2OAc, CH2C6H4OH-4, CH2C6H4OMe-4, I, Br, CH2O2R1; R1 = alkyl, aryl, R (un)substituted NH2] in a formulation. Thus, anisole was reacted with 6-(hydroxymethyl)fulvene in the presence of BF3-etherate, producing I (R = CH2C6H4OMe-4), which demonstrated a 48-h IC50 against 8392 cells of 7143 nM/L.
IT **158440-71-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of acylfulvene-analog antitumor agents)
RN 158440-71-2 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-(hydroxymethyl)-2',4',6'-trimethyl-, (6'R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



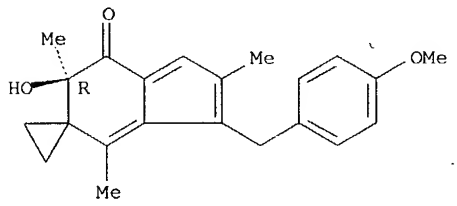
IT **158440-74-5P 158440-75-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of acylfulvene-analog antitumor agents)
RN 158440-74-5 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(4-hydroxyphenyl)methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 158440-75-6 CAPLUS
CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 6'-hydroxy-3'-[(4-methoxyphenyl)methyl]-2',4',6'-trimethyl-, (R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 75 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1991:648087 CAPLUS
DOCUMENT NUMBER: 115:248087
TITLE: Illudin analogs as anti-tumor agents
INVENTOR(S): Kelner, Michael J.; McMorris, Trevor C.; Taetle, Raymond
PATENT ASSIGNEE(S): University of California, Berkeley, USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9104754	A2	19910418	WO 1990-US5614	19901002
WO 9104754	A3	19911212		

W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MC, MG, MW, NL, NO, RO, SD, SE, SU
RW: AT, BE, BF, BJ, CF, CG, CH, CM, DE, DK, ES, FR, GA, GB, IT, LU, ML, MR, NL, SE, SN, TD, TG

CA 2067365	AA	19910404	CA 1990-2067365		19901002
AU 9067295	A1	19910428	AU 1990-67295		19901002
JP 05503077	T2	19930527	JP 1990-515522		19901002
EP 565519	A1	19931020	EP 1990-916968		19901002
EP 565519	B1	19960828			
R: AT, BE, CH, DE, DK, ES, FR, GB, IT, LI, LU, NL, SE					
IL 95875	A1	19941021	IL 1990-95875		19901002
AT 141802	E	19960915	AT 1990-916968		19901002
ES 2091249	T3	19961101	ES 1990-916968		19901002
PRIORITY APPLN. INFO.:			US 1989-416395	A	19891003
			WO 1990-US5614	A	19901002

OTHER SOURCE(S): MARPAT 115:248087

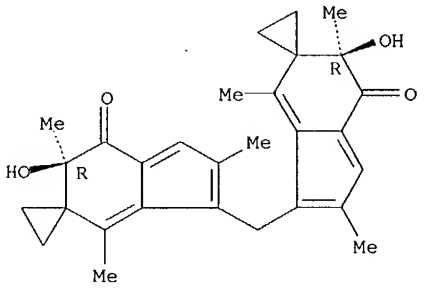
AB Illudin S or illudin M analogs I or II (R1 = H, alkyl, alkoxy; R2 = alkyl; R3 = alc., ester) are administered to inhibit tumor cell growth. Dehydroilludin M (III) was prepared by treatment of illudin M with pyridinium dichromate. The IC50 of III against HL-60 leukemia cells was 46 nm. III was effective at inhibiting tumor growth in mice. Structure-function studies of illudins and derivs. identified 3 critical sites for illudin toxicity.

IT **137295-69-3P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as neoplasm inhibitor)

RN 137295-69-3 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-methylenebis[6'-hydroxy-2',4',6'-trimethyl-, [R-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L5 ANSWER 76 OF 76 CAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER:	1971:529055 CAPLUS
DOCUMENT NUMBER:	75:129055
TITLE:	Fulvenes derived from illudin S
AUTHOR(S):	Weinreb, Steven M.; McMorris, T. C.; Anchel, Marjorie
CORPORATE SOURCE:	Dep. Chem., Fordham Univ., Bronx, NY, USA
SOURCE:	Tetrahedron Letters (1971), (38), 3489-91 CODEN: TELEAY; ISSN: 0040-4039
DOCUMENT TYPE:	Journal
LANGUAGE:	English

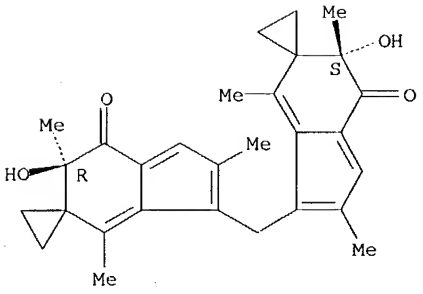
AB Illudin S (I) is treated with H2SO4 to give an acyl fulvene dimer (II) via a reverse Prins reaction; a fulvene (III) is the reaction intermediate. I is treated with cold H2SO4 to give II; the dimedone derivative of H2CO and III are isolated from the reaction mixture III is obtained by a reverse Prins reaction of I and reacts with the H2CO liberated to give II. III is treated with H2SO4 containing H2CO at 0° to give II. NMR, uv, ir, and mass spectral data are given for II which is optically active; mass spectral data are also given for III.

IT **33910-65-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 33910-65-5 CAPLUS

CN Spiro[cyclopropane-1,5'-[5H]inden]-7'(6'H)-one, 3',3'''-methylenebis[6'-hydroxy-2',4',6'-trimethyl-, (-)- (8CI) (CA INDEX NAME)

Rotation (-). Absolute stereochemistry unknown.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OH
S
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HO
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